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The American Heart Journal

VOL. 20 DECEMBER, 1940 No. 6

Original Communications

NOMENCLATURE AND DESCRIPTION OF THE ELECTROCARDIOGRAM

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NEW YORK, N. Y.

THERE is at present a regrettable confusion in the application of Einthoven's terminology for the peaks of the electrocardiogram (Hurxthal,[1] Shookhoff and Douglas,[2] Vega and Quero[3]). This is especially true of the QRS group, and, to a lesser extent, of the T wave. It is unfortunate that our terminology should be indefinite, for the method most used for describing and comparing the curves involves measurement of the height of the peaks. It is necessary, therefore, that the peaks be similarly named by all who are studying them; for this reason, I wish to suggest the adoption of certain principles of nomenclature which can be readily applied.

Einthoven at first designated the usual, large, upward deflection of the QRS group as R, and applied the term Q to the downward deflection which often preceded it, and S to the downward deflection which often followed it. When he came to compare records obtained by three leads from the same subject he encountered difficulties in applying this terminology to the peaks which appeared in the different leads. It was apparently his idea at this time that R should be the name of the most prominent peak of each lead, and that the terms Q and S, respectively, should be applied to the portions of the QRS group preceding and following this peak. He referred repeatedly to the most prominent peak in Lead I or Lead III as an R wave, even when this peak was directed downward, and occasionally referred to an upward Q or S wave. In 1908, he[4] published the figure, reproduced here as Fig. 1, which shows an upward Q_3 and a downward R_3. In this same article he suggested that the formula Lead II – Lead I = Lead III might be used for the identification and naming of the corresponding peaks in the different leads. He stated that "although this method might appear simple enough, yet difficulties would arise in applying it, especially because the waves indicated by the same letters often fail to occupy identical phases of the heart cycle."

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Quite evidently he recognized at this time the fallacy of supposing that similarly named peaks in different leads would always arise from the same potential produced by the activity of the muscle. Possibly it was the further development of this thought which led him,[5] in 1916, in referring to Lead III of a record with typical left axis deviation of QRS, such as Fig. 1, to say that "inasmuch as there is no reason to regard this large negative peak (in Lead III) as either R or S, we encounter a real difficulty in searching for the similarly named peak in the other leads. We avoid this difficulty if we consider the QRS group as a whole, and take the highest or lowest point of the group in the three leads as the object of our measurement." The measurement referred to was to be used for determining the electrical axis of the most prominent peak of the QRS group. In his later writings he showed little inclination to name the individual peaks. Among the illustrations of his Harvey Lecture, in 1924, he included a record in which Lead I and Lead III were quite similar to those of Fig. 1, and marked the QRS group of Lead III simply as QRS, in spite of the fact that naming the peaks would not have been difficult in this case if his original procedure of calling the largest deflection R had been followed.

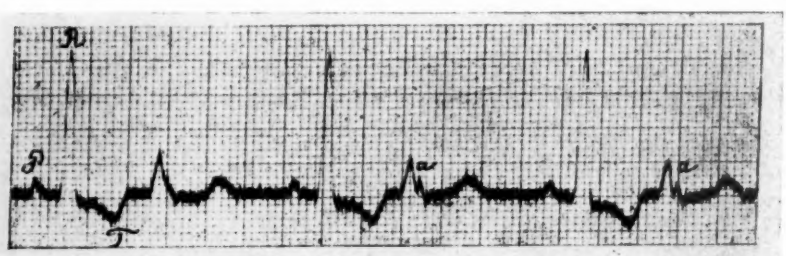

Fig. 40. *S. K.* Atypische Herzkontraktionen. Ableitung I.

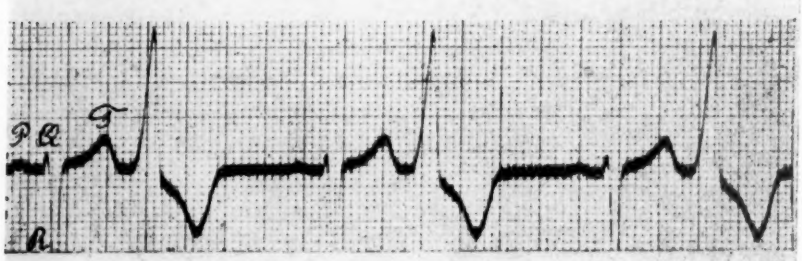

Fig. 41. *S. K.* Atypische Herzkontraktionen. Ableitung III.
Absz. 1 mm = 0,04 Sek. Ordin. 1 mm 2×10^{-4} Volt.

Fig. 1.—Showing Einthoven's early use of the nomenclature of the QRS group (from Weiteres über das Elektrokardiogramm, *Arch. f. d. ges Physiol.* 122: 517, 1908). Note particularly the upward Q and downward R in Lead III.

Einthoven's terminology, as he first used it, seemed to imply that peaks of the same name in different leads should represent the same current within the heart. As he himself pointed out, however, this

implication was not justified, for the different peaks of the QRS group in the three leads rarely occur at exactly the same instant during the cardiac contraction, and are sometimes markedly separated in time. The similar name does not indicate the same action current of the heart. This feature may be demonstrated clearly if two or more leads are taken simultaneously. Fig. 2, which is reproduced from Einthoven,[6] affords an excellent example of how peaks named alike by Einthoven's method may fail to represent synchronous portions of the QRS group. The peaks of Q_2 and Q_3 occur during the ascent of R_2, and when R_3 has reached only half of its height. The peak of S_1 occurs when the descent of R_2 is only half completed, and the total duration of S_1 is represented in the descending portion of R_3.

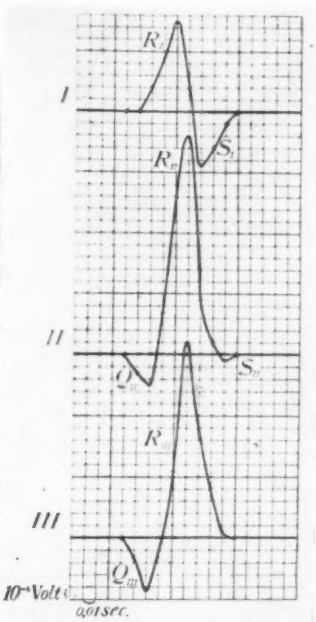

Fig. 16 Konstruktion der *QRS*-Gruppe von Fl. bei den drei Ableitungen. Jede Ordinate entspricht identischen Phasen einer Herzperiode. Abszisse 1 Skalenteil = 0,01 Sek.; Ordinate 1 Skalenteil = 10^{-4} Volt.

Fig. 2.—Construction of the QRS group by the three leads. (From *Arch. f. d. ges. Physiol.* **150**: 291, 1913.)

Einthoven's nomenclature, in this record, would apply the name S to a peak in Lead I resulting from potentials which are a part of R in Lead III, and the name Q, in Leads II and III, to peaks resulting from potentials which are a part of R in Lead I. It also fails to indicate, by name, the deflections in Leads II and III caused by the potential which produces S_1, or to indicate in Lead I the potential which produces the deflections Q_2 and Q_3. In each case, the value in question is repre-

sented in the ascending or descending limb of the R wave. It would have been evident that this was the case if Einthoven's formula of lead values had been applied to the standard electrocardiogram of this patient. The negative value of Q_3 must have a corresponding positive value in Lead I of at least the difference between Q_3 and Q_2, and the negative value of S_1 must have a corresponding positive value in Lead III of at least the difference between S_1 and S_2. Thus, the manner of development of the heart's potential can often be roughly ascertained by the application of Einthoven's formula to the peaks of the three leads, and the actual names which he would have applied to the peaks do not give additional help in understanding it. On the contrary, if they be taken too literally, the impression that like names in different leads represent like potentials will actually become misleading. It is possibly for this reason that he came to avoid naming the individual peaks, and to speak of the QRS group as having its "chief deflection" in one or another direction.

Lewis and Gilder,[7] in 1912, published a series of measurements of human electrocardiograms, and, in this report, as well as in his other writings,[8] Lewis deviated somewhat from Einthoven's usage in lettering the peaks of QRS. He indicated only downward peaks by the letters Q and S, and only upward peaks by the letter R. With this method of naming the peaks, the upward deflection of Lead I might be called R, while a corresponding, synchronous, downward deflection in another lead, caused by the same potential, might be called either Q or S, depending upon whether it preceded or followed the upward deflection of that lead, which would be called R. When the upward deflection was notched, or when there were two upward peaks, Lewis simply called the deflection a notched wave.

Lewis' method of lettering the peaks failed, as did Einthoven's, to take into account the potential contributing to the ascending and descending limbs of the deflections. It differed from Einthoven's earlier ideas in that it avoided any suggestion of giving the same name to related potentials in different leads. It was a purely arbitrary terminology which carried only an implication of direction, whether upward or downward, and, in the case of the terms Q and S, of time relative to the upward deflection, which was always called R.

Although Einthoven's method was more widely used at first, the majority seem to have preferred to follow Lewis' frankly arbitrary method of naming the individual peaks, rather than Einthoven's more superficially logical one. Although some have objected that Lewis' method also may interfere with an understanding of the events of the QRS group because the same potential may cause peaks with different names in different leads, no such confusion should arise if the nomenclature is understood to be entirely arbitrary and not to imply any relationship between peaks of the same name. In such an arbitrary system there must not be any implication that similar names have a

similar clinical significance, for then, in occasional cases, when the clinical significance is not the same, we find ourselves in a quite illogical position. Because Einthoven's method, as he first used it, implied that similarly named peaks have a similar origin, and because it can be demonstrated that such peaks in different leads do not usually have a similar origin, it seems best to avoid Einthoven's method of naming these peaks, and follow Lewis' simpler and more arbitrary method of applying Einthoven's letters.

Neither of these authors continued to expand his terminology sufficiently to indicate how it should be applied to certain unusual varieties of QRS which are encountered. It seems necessary that this should be done in order to avoid further confusion; and, therefore, an expansion of Lewis' modification of Einthoven's electrocardiographic terminology is here submitted.

A QRS group with two upward peaks separated by a downward one has commonly been referred to as an M-shaped complex. Likewise, when there are two or more upward peaks and two or more downward ones, the term vibratory QRS group has often been used. These terms are sufficiently descriptive to be easily applied, and may be useful for general purposes, but they make it impossible to refer to the extra peaks specifically, or to measure them. It is therefore suggested that, when more than one upward deflection appears, the first should be called Ra, and the subsequent ones Rb, Rc, etc., as occasion arises. A downward deflection preceding the first R would be referred to as Q, and the first downward deflection following the first upward deflection would be called S if there were only one, and Sa if there were more than one. Subsequent downward peaks would be called Sb, Sc, etc., as in Fig. 3.

In describing precordial leads, the same arbitrary terminology of QRS can be applied with equally satisfactory results if it be clearly understood that here the peaks of the same name are even more dissimilar in origin than in the standard leads. Nor need records from patients with congenital dextrocardia lead to confusion, for Lead I is just as truly a reversal of the ordinary Lead I if we call the first deflection Q and the second R as if we called them inverted R and S waves, respectively. To do the latter is not, in our opinion, good practice, for it implies that the names of the peaks have a definite meaning.

There has not been a proper agreement as to the naming of the waves of a QRS group like those in Fig. 3*C*, which shows, first, a very small upward deflection, i.e., 1 mm., or less, followed by a sizable downward peak and another upward peak. Some would disregard the small, initial, upward peak and call the downward one Q and the second upward one R. There is a very real objection to this procedure, in that it demands a definition as to exactly what size must be reached by the initial deflection before it may be called R. It seems more simple, and, therefore, better, to call any upward deflection R, and to name the other peaks in proper sequence. To call such a QRS an M complex is unsatisfactory, as has been said, because this does not allow of measurements.

Usage is also divergent when the QRS group is entirely below the isoelectric level, with no upward peak which could be called R, as in Fig. 4*D* and *E*. This downward peak has previously been called S^0, because in limb leads such records are most frequent with right or left axis deviation of QRS, and because the downward peak in Lead I with right axis deviation, and, in Lead III, with left axis deviation, is usually an S. This S is often preceded by a small R and as in Fig. 4*C*, such an R may disappear during one phase of respiration, leaving only a downward deflection. It is because of the frequency of such records, and because they are often associated with ventricular hypertrophy caused by valvular disease, that the author has previously advocated the use of the letter S for the peak of a QRS group which has no upward deflection. Such records are obtained almost as commonly from patients with valvular disease as from patients with coronary arteriosclerosis. In a group of seventeen such records, selected from a large clinic series, seven were from patients with disease of the mitral or aortic valve, or both, and the remainder from patients with coronary arteriosclerosis or hypertension. Furthermore, Durant, who called such a QRS group Q, has found that if patients with such records are excluded from a group in which Q_1 is large, more patients with valvular disease will be excluded than will remain.[10]

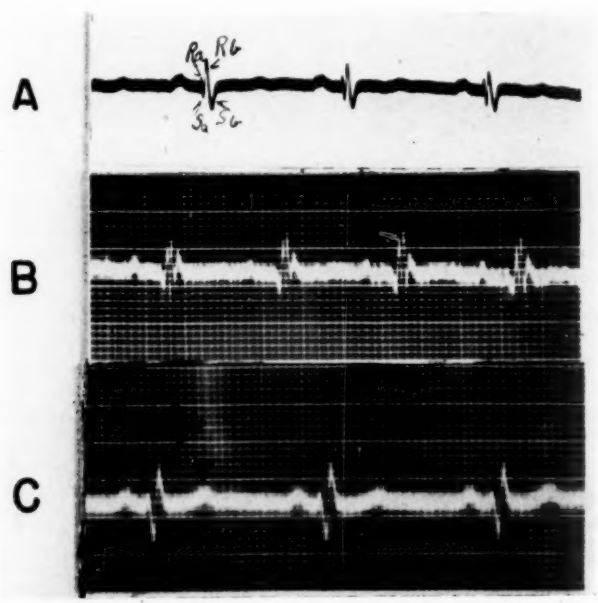

Fig. 3.—Illustrating the nomenclature of M complexes in *C* and of the vibratory QRS group in *A* and *B*.

In spite of the above considerations, many physicians have called such a wave Q, thinking that it warrants this title because it is the first downward deflection of QRS. Neither Einthoven nor Lewis used the letter Q

in this way; both of them designated Q as a downward deflection which preceded R. Also, it has been suggested that these waves should be called Q because they are often found in clinical conditions which are likely to be associated with well-marked Q waves followed by an R. This reason violates the principles of an arbitrary nomenclature. In view of the present divergent usage in naming these downward QRS deflections, it seems very important to reach an agreement. This downward deflection, like any other QRS group, contains the elements of the Q, R, and S which may appear in other leads of the record. It seems

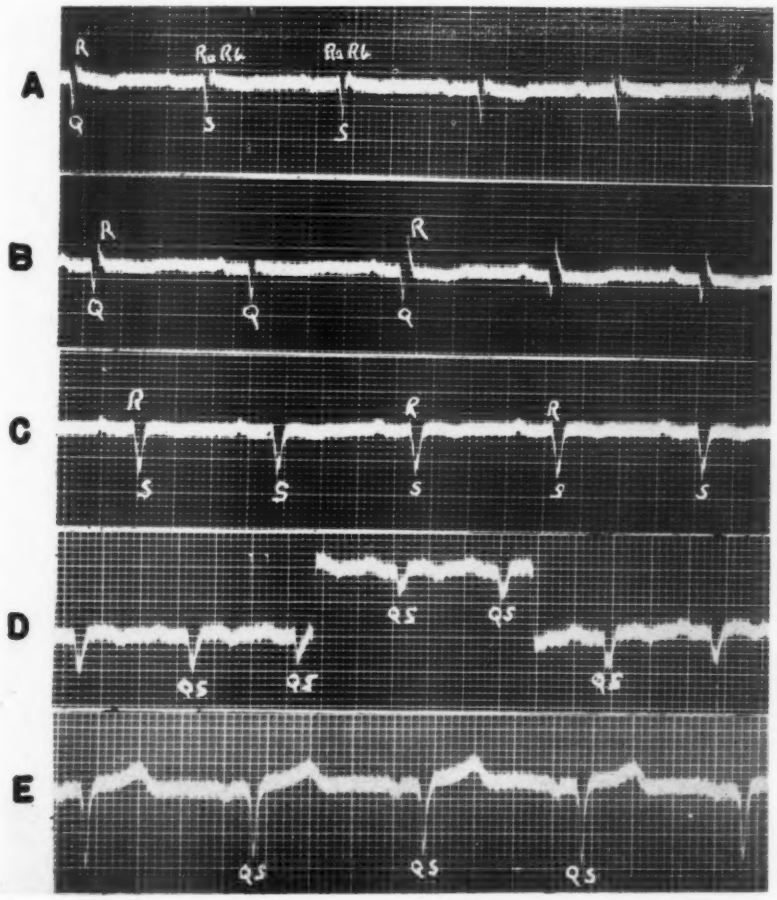

Fig. 4.—The nomenclature of downward deflections. Records *A* and *C* show downward waves which should be called S. Record *B* shows downward waves which should be called Q. Records *D* and *E* show downward waves which should be called QS.

advisable, because of the current lack of agreement concerning the name for such waves, and in order to distinguish them from others whose apices are followed by an R wave, or are preceded by an R wave, to call these deflections QS. This would indicate that they contain the elements of both peaks, and that there is a possibility that in records taken at

another time a small R might appear and indicate definitely which name should have been attached to the wave; moreover, it may be possible, by thus separating these records from those with a definite Q (followed by R) and a definite S (preceded by R), to come to understand more clearly what their clinical significance may be.

If it is to be called QS, there must not be any upward deflection, no matter how small, either preceding or following this downward wave. If such a deflection precedes, as in Fig. 4*C*, the downward peak must be called S. If a small upward deflection follows it, as in the first cycle of Fig. 4*A*, it must then be called Q. In records with a small R which appears and disappears with respiration, the disappearance of R may lead to a change of the name of the downward deflection, as in Fig. 4*A*, *B*, and *C*. In order to avoid this, it is advisable to retain throughout the lead whichever name, Q, S, or QS, would belong to the downward deflection in the majority of the complexes.

The use of the term notching should be restricted to doubled or split waves, the peaks of whose notches do not cross the isoelectric level. Should the isoelectric level be crossed, each of the resulting peaks should take a name of its own, as in Fig. 3*A*. Notching of the QRS group is an important feature and should be described exactly. It should be stated that it occurs at + or − so many millimeters on the descent or ascent of the wave, and the lead should be designated, e.g., at −5 mm. on the descent of S_2. This exact description is needed, for it has been observed that notching of QRS in certain situations in relation to the peaks is commonly associated with myocardial damage.

Lesser grades of disturbance of the course of the ascending or descending limb of a peak are called slurring. With this in mind, the normal form of the peaks or QRS must be especially noted; often the first deflection, as it turns away from the P-R level, does so in a rather gradual slope, and the line at this point is broader, and therefore more slurred, than the subsequent course of the wave, which becomes more abrupt and steeper in its further course toward the peak (R_1, Fig. 1; QS wave, Fig. 4*E*). At the peak of a wave the rate of ascent or descent usually is less abrupt than in the remainder of its course, so that one often sees, just before or after the peak, or perhaps in both places, a thickening of the line to which the term slurring may be applied, as in R_1 of Fig. 1. In other records a deflection of small size will produce what appears as a rather uniformly thickened line, when compared to the thinness of the line producing larger deflections. This may be observed in R_3 (Q_3) of Fig. 1 and in the first downward deflection of Fig. 3*B*. Since this is a uniform thickening of the line, it may not be comparable to those thickenings which occur in only a portion of one side of a wave, but until more definite knowledge on this point is available, it seems best to apply the term slurring to this feature. As QRS comes to an end at the R-T

or S-T transition, the slope is often more gradual and the line more slurred than in other portions of the peak. This is seen in R_1 and S_3 (R_3) of Fig. 1.

It is known that slurring of the peak of a wave or at the beginning or ending of the QRS group may occur normally, so that the location of the slurring must be noted as an aid in deciding whether it has any pathologic significance. It should be described in a manner analogous to that used for notching, namely, that it is found a certain number of millimeters from the zero level and on the ascent or descent of a certain wave. In the present state of our knowledge it is possible to attach more definite significance to slurring which does not occur at one of the three normal sites than to that which does. We cannot distinguish the borderline between a normal and an abnormal degree of slurring in these normal locations.

The "duration of the QRS group" has not been subject to misinterpretation, but insufficient attention has been paid to the fact that the duration varies in different leads. Reference to Fig. 2 will show that the duration of QRS is shorter in Lead I of this record than in Leads II and III. Inasmuch as the duration of QRS indicates how much time it takes for the contraction wave to spread over the ventricular muscle, the longest QRS in any given electrocardiogram must be the nearest approach to the actual time of spread. If QRS is shorter in one lead than in another, it must be because a portion of the QRS group is isoelectric in that lead, as in Lead I of the figure. Inasmuch as different records will be found to show the longest QRS in different leads, it is obvious that no one lead can be selected to indicate the duration of the QRS group, and that it should be measured in all leads and the longest measurement used. The duration of the R wave alone, will, of course, have little physiologic significance.

Similar considerations lead to the conclusion that measurements of the duration of any part of the electrocardiogram should be made in all three leads, and that the longest measurement should be taken to indicate the actual duration. This applies to the P wave, the P-R interval, QRS, the Q-T interval, and the T wave. In following this procedure, occasional records will be found in which the P-R interval is prolonged by 0.01 or 0.02 sec. because of the inclusion of an initial isoelectric portion of QRS in this interval. Such is the case in Lead I of Fig. 2. It may be suspected in clinical records when one lead shows a shorter QRS duration and a longer P-R interval than the others.

The QRS group passes over more or less abruptly into the T wave. The portion of T immediately following the R-T or S-T junction has often been referred to as the R-T or S-T interval or segment. For purposes of nomenclature we may speak of this as the S-T junction or segment, irrespective of what name may be applied to the last peak of QRS, just as we speak of the P-R interval, irrespective of the name of the first peak of QRS. The ending of the S-T segment cannot be definitely

indicated, for it passes quite gradually into the peak of T. It is actually the first limb of the T wave. It seems important from the point of view of nomenclature to refer to the whole of the final deflection as the T wave, and to speak of its beginning as the S-T junction.

In most electrocardiograms the S-T junction is effected by a definite change in the inclination of the curve toward the isoelectric level, so that within less than 0.01 sec. the R or S wave may be said to end and the T to begin, forming a more or less sharp angle at this point. Other electrocardiograms may show a gradual change in the inclination of the curve, so that R or S, as in Fig. 1, may curve gently into the beginning of T, sometimes taking 0.04 sec., or more, to complete the transition. These two types of S-T junction are not separate and distinct, but represent the two extremes of the various forms which may be encountered; various degrees of sharpness of the resulting angle at the junction will be observed. One or more leads of the record may show a sharp S-T transition and the remainder a less sharp transition. If, however, several cycles are carefully inspected, it is usually possible, as a result of the variations in the complexes which occur with respiration, to discover in even the most gradually curved transition a point which may be called the S-T junction.

This junction should be described as being positive or negative, in relation to zero. Special attention should be given to an observation made by Lewis, in 1912. The deflection of the P-R level is caused by auricular activity which continues, although diminishing, for 0.36 sec., or more, after the beginning of P, so that this in effect establishes a new zero level for the deflections of the QRS group and the S-T junction, from which new level their deflections should be measured. Usually, this deflection is less than 1 mm., but in certain records it may reach a magnitude which makes it important.

Having described the position of the S-T junction in relation to this zero, we must still describe the T wave, i.e., the whole of the final deflection of the electrocardiogram. It is commonly a single wave whose first limb is irregularly convex toward its base; that is, it does not follow the arc of a circle, and often shows a more or less straight portion.

The term diphasic has been commonly applied to certain peculiar forms of the T wave, but there has not been general agreement as to what this term should imply. In general, a movement is said to be diphasic when it has a positive and a negative phase, or vice versa, in reference to any given point. It makes a difference, then, whether we consider the deflections of T in relation to the zero level of the record or to the beginning of T itself, i.e., the S-T junction, which might be at zero, or above or below it. Since electrocardiographic deflections usually are considered as upward or downward in relation to the zero level of the record, it seems best to relate the T wave to this level, also. If there is an apex above the zero level and also one below it, the wave may be

described as diphasic, and the signs + and – may be used to indicate the order of occurrence of the upward (+) and downward (–) peaks; that is, + – or – +. Occasionally a T wave may be found which shows as many as three apices; such a wave might be called triphasic. The term diphasic, however, will be applicable to waves of such varied forms that it does not afford a description of T which would be satisfactory in sorting out waves of similar appearance.

Since further detail in description is desirable, it is recommended that the use of this term be amplified as described below. Having noted the position of the S-T junction as + or – or isoelectric, we must next indicate the number of apices shown by the T wave, using the terms monophasic, diphasic, or triphasic. We must now describe the character of the curve between the S-T junction and the first apex of the T wave. It may be concave toward zero, horizontal, or convex toward zero, and may occasionally leave zero at an angle in a quite straight line. If the line is at first horizontal it always changes to a curve before reaching the apex, and the direction of the curve is determined by that of the peak, so that this curve need not be especially described. The first peak of T should be described as + or –, and measured in millimeters. If no peak appears, T should be described as isoelectric. If there are more than one apex, they should be spoken of as Ta, Tb, and Tc, and their relation to zero indicated as + or – so many millimeters. The curve following the first apex of T need not be described, for it is so dependent for its form upon the position of the different apices in relation to zero and to the beginning of T that it follows from a description of these points.

The description of the T wave will then comprise the following:

S-T junction: deflection +, 0, or –, in mm.

T wave: isoelectric, monophasic, diphasic, triphasic.

Course: toward first apex of T { horizontal / concave (toward zero) / convex (toward zero) / straight }

Apices: T, or Tb (deflection +, 0, or –, in mm.)
Tc

For example, T_1 of Fig. 1 would be described as follows: S-T junction –1 mm., T monophasic, course convex, –4 mm. T_3 of this figure would be described as S-T junction +1 mm., T monophasic, course convex, +4 mm. The T wave of Fig. 4*D* would be described as S-T junction +0.5 mm., T diphasic, course concave, Ta = +0.5 mm., Tb = –0.5 mm.

There are records in which it is difficult to mark the ending of T and in which this wave may appear to be prolonged and diphasic or triphasic. This is usually caused by fusion with U, and this fact can be recognized if the duration of T is measured in another lead in which T shows a more definite termination. If this measurement of duration be applied to the doubtful lead, it will be seen that what was thought

to be the prolongation or the final apex of T has really occurred after the end of this deflection, and is therefore either the beginning of U or the peak of U.

The P wave may be described in a manner analogous to that proposed for T. It may be directed upward or downward, may be diphasic or isoelectric, and may show notching of one of its limbs or of the peak. Its description and measurement should follow the general lines suggested for T.

SUMMARY

In view of the present confusion regarding the terms to be applied to the peaks of the electrocardiogram, the usage of Einthoven and of Lewis has been reviewed in the hope of finding a reasonable solution. Lewis' modification of Einthoven's terminology is recommended.

Suggestions are made for naming the peaks of certain types of QRS not particularly mentioned by Lewis, namely, the M complex, the vibratory QRS, and the solely downward deflection.

A method of describing notching and slurring of QRS is outlined, and certain features of the measurement of the duration of P, QRS, and Q-T are emphasized.

A definition of the term diphasic is suggested, to be applied to the P and T waves; also, a method of describing these waves which is considered adequate for statistical grouping is presented.

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THE USE OF THE CATHODE RAY* FOR RECORDING HEART SOUNDS AND VIBRATIONS

I. Studies on the Normal Heart

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THE mechanism of production of the heart sounds and conditions influencing their character have interested physiologists and clinicians for many years. During that time numerous and various instruments were devised for recording them, and a great many observations on the heart sounds were made. A thorough review of the historical developments in this field has been presented by Bierring and his co-workers[1] and need not be repeated here. Many of the instruments more recently developed[2-11] for the graphic registration of the heart sounds embody a string galvanometer as the recorder, and use microphones and amplifiers of various design; some utilize other electrical or mechanical devices for recording the sounds. Observations made with these instruments have yielded valuable information concerning the heart sounds, especially as regards the time of their occurrence in the cardiac cycle, as well as some factors in their production, and the time and duration of murmurs.

Clinicians have long been aware that certain fundamental changes in the heart tones, irrespective of adventitious sounds that are difficult to interpret, may appear in various kinds of heart disease and in other derangements of the circulatory system. It would seem advantageous, therefore, to record all of the vibrations, whether audible or inaudible, which are set up by the heartbeat, so that finer changes in the fundamental heart sounds, as well as the time and character of adventitious sounds, might be detected and studied.

PHYSICAL CONSIDERATIONS

Any vibrating object transmits its movement to the media within which it rests. This movement may be picked up and recorded by mechanical means, or by the ear. Vibrations may be of many types. They may be discerned by the ear if their frequency is sufficient, or they may not be acoustically recognized at all. There are two factors in the thresholds of hearing. One is the energy threshold, which an audible vibration must exceed to be heard, and the other is the frequency threshold, below which a continuous vibration will not be heard.

Vibrations with a frequency and intensity that enable them to be heard are sound stimuli. A musical sound is made up of a fundamental, or basic, frequency, together with a number of higher vibration frequencies which are

*The cathode-ray "vibrocardiograph" was built by the Burdick Corporation.

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called harmonics. Continuous vibrations of sufficiently low frequency will not be heard, regardless of volume or energy level, and vibrations of a frequency in the audible range must reach a certain intensity in order to be heard. The usual heart sound does not have a musical pitch and is essentially a noise. It is made up of a group of different, continuously changing fundamentals and inharmonic partials. Because of these characteristics, a heart sound is often hard to describe satisfactorily.

The ordinary stethoscope, as a medium for picking up heart sounds, has certain disadvantages. A consideration of the character of the sounds heard through the stethoscope involves dealing extensively with acoustics; the stethoscope does not transmit to the ear all of the frequencies of the heart sounds in undistorted form. For example, in a stethoscope in which a column of air is the transmitting medium, the column, once set in motion, may continue to move, thus introducing vibrations to the ear which have not been produced by the heart. In such an apparatus there is no means of preventing this action.

DESCRIPTION OF CATHODE-RAY "VIBROCARDIOGRAPH"

Since it seems possible that information may be gained by recording vibration frequencies lower than those of the acoustic spectrum, an instrument was designed to obtain high fidelity of reproduction of the vibrations produced by the beating heart, rather than to select or emphasize those which are appreciated acoustically. In order to attain this result, air transmission in any form was avoided. In making a record, a water-filled capsule, three inches in diameter and a quarter of an inch in thickness, whose two flat surfaces consist of thin rubber membrane, is placed on the chest, and the pickup unit is firmly strapped in contact with the outer surface of the capsule. The spring spider supporting the button of the pickup is thus kept under strain, and the vibration frequency of the system is correspondingly increased. A specially constructed, dynamic type microphone, with an extremely light moving unit, is used as the pickup. Currents from this pass to an amplifier, and, from the output of the amplifier, connections are made to the vertical or Y-plates of two cathode-ray tubes. One of these, which has a five-inch, long-persistence screen, is used as a viewing tube; the other, which has a three-inch, short-persistence screen, is enclosed in a lighttight housing and is used for photographing the vibrations on 35 mm. bromide paper. Time is recorded on the bromide paper by a small gas tube, flashed by an electric clock motor at the rate of five times a second. In the case of the viewing tube, a tripping device moves the spot across the tube face at a rate which may be synchronized with the heartbeat. By employing the two cathode-ray tubes in this manner, it is possible to watch spot movements on the viewing tube as long as one wishes, and to take records only when desired.

Studies were made to ascertain the fidelity of response of the amplifier and pickup unit. Using a beat frequency oscillator, sine waves were applied to the amplifier. This was found to have a drop off in transmission of less than 2 per cent between five cycles and fifteen hundred cycles per second. In testing the frequency response of the microphone, the pickup unit, without the water capsule, or with the capsule in firm contact, was activated by tuning forks of various frequencies. At frequencies of 50 to 500 d.v. per second, no obvious irregularity of response was introduced (Fig. 1 *A*, *B*, *C*, *D*). The free period of the microphone button, with the unit held inverted and free in air and then gently tapped, was, for two units of slightly different design, 175 and 190, respectively (Fig. 1 *E* and *F*). When the microphone unit was held in firm contact with one surface of the capsule, and the lower surface of the capsule left free, tapping the unit or the water capsule then caused irregular oscillations with various obvious component fre-

quencies (Fig. 1 *G*). This merely indicates the necessity of having the capsule filled with water (containing no air bubbles) and in firm contact with the chest on the one side and the microphone unit on the other. Under these conditions there is no such random movement of the water in the capsule.

Since satisfactory synchronization of sound records and electrocardiograms depends upon adequately controlled time signals, the same circuit was used to activate flashing lamps for the two records simultaneously. To check against possible error caused by parallax, in the case of the sound records part of the voltage acting on the flashing tube was led through small condensers to the amplifier circuit, making sharp breaks in the record with each tube discharge. It is to be seen that there is no significant parallax error (Fig. 1 *H*). Similar precautions were taken in the case of the electrocardiographic records.

It is our belief that, at the paper speed used (97.5 mm. per second), the instrument is more than adequate to record frequencies which can be recognized as discrete waves over a range of 5 to ca. 250 per second. It seems probable that it is adequate to record, with little or no distortion, such higher frequency components produced by the beating heart which contribute to the acoustic qualities observed with the usual stethophones.

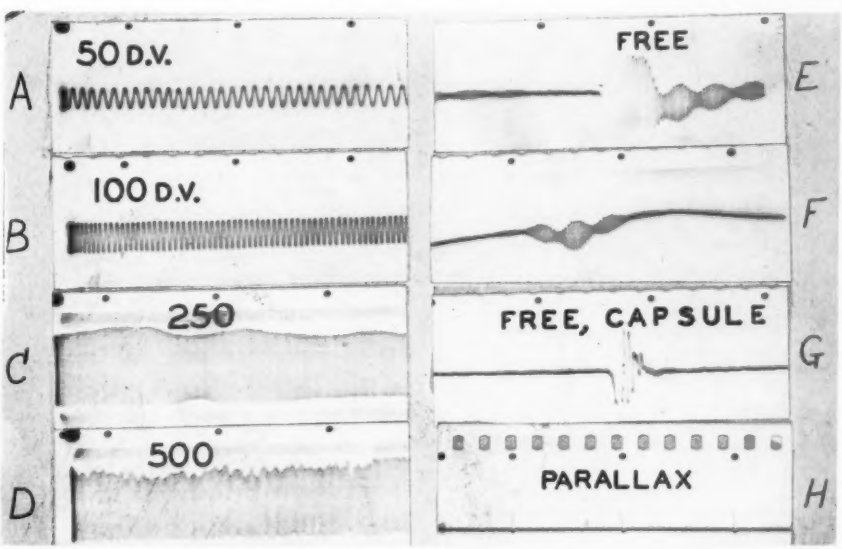

Fig. 1.—*A*, *B*, *C*, and *D* illustrate the response of the amplifier and cathode ray, when applied to a beat frequency oscillator, at 50, 100, 250, and 500 cycles per second. *E*, *F*, and *G* show the response of the microphone to gentle tapping with and without water capsule (see text). *H*, Record testing parallax in the time signalling device.

To record the cardiac vibrations the patient is placed in a recumbent position with his arms at his sides. The microphone is placed over the heart. Tracings from the aortic, tricuspid, mitral, and pulmonic areas are usually made. Because of the fact that the most intense vibrations may be inaudible because of low frequency at a given point, it is often desirable to place the microphone in several positions on the chest wall in order to find the point of greatest vibration intensity, as noted on the fluorescent screen of the viewing tube. Additional records may be made from any other point desired. Each patient was cautioned not to speak, cough, or move during the recording, and care was taken to induce patients to relax. In this way, the introduction of artifacts into the curves was avoided. In accord-

ance with standard practice, electrocardiograms (Lead II) were taken simultaneously with the vibrocardiograms, with which they were synchronized by means of the lighting mechanism described above.

CHARACTERISTICS OF CARDIAC VIBRATIONS

Many different types of curves have been obtained from normal and abnormal hearts. A cursory analysis (true analysis of curves of this sort requires considerable mathematical calculation which will not be included here) shows that there are many differences in the vibrations. Variations in frequency, frequency rate, amplitude, and conformity of the curves were noted.

The wave shape of the vibrations from the normal and diseased heart, as shown by the vibrocardiograph, is a graphic summation of all of the waves which are present. If the apparent frequency is changing in a given "heart sound," we know that either inharmonic partials are present or a new frequency is being generated; that is, if a new wave is being generated, it may effect a complete change in frequency and shape of the wave under observation. If higher harmonic or inharmonic waves of sufficient amplitude are present, they may appear as more or less obvious, small wavelets, superimposed on the large fundamental waves.

In this communication we shall confine ourselves to a brief discussion of normal cardiac vibrations. Figs. 2, 3, 4, and 5 are typical examples of curves obtained from subjects who had no demonstrable cardiac, pulmonary, or bony thoracic abnormalities.

Conformity of Waves and Time of Their Occurrence in the Cardiac Cycle.—The appearance of the wave complexes varies with the point on the chest from which they are recorded. The first and second wave groups (representing the first and second "heart sounds") are easily identified by the longer duration and sharper spiking of the second wave complexes, and by correlating the time of their occurrence with the electrocardiogram. The first sound complex begins with one or two waves of a smooth character which fall between the crest of the P wave and the upswing of the R wave of the electrocardiogram. These waves occur during auricular systole, but are of a frequency (below forty cycles a second) too low to be heard. A sudden upward or downward movement of the cathode-ray record falls before, or near, the peak of R, and represents the onset of the audible portion of the first heart sound. Thereafter comes a series of gross waves of irregular character, varying from three to six in number, and often punctuated by a series of small, sharp points which represent the interpolation of many wavelets of higher frequency. Depending on the number of deflections in the group representing the first disturbance, the complex may extend well through the R-T interval.

The second group of deflections begins and ends more abruptly than the first. In records taken by this method, the onset of the second com-

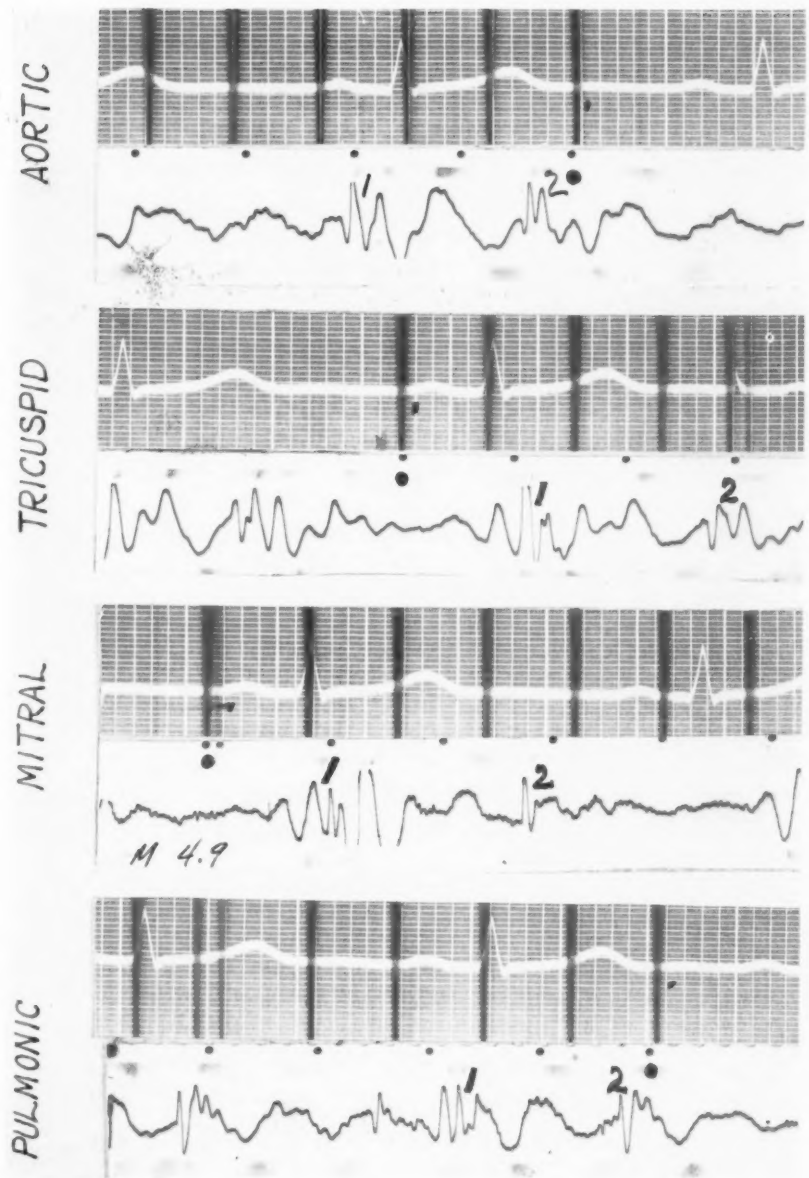

Fig. 2.—W. P., white man, aged 40 years. Sthenic habitus; no cardiac or pulmonary abnormalities; heart tones of "normal quality" at all auscultation areas; no adventitious sounds. The first and second heart sound complexes are designated *1* and *2* on the record.

The electrocardiographic and stethographic tracings were recorded on separate instruments at slightly different paper speeds. Synchronization was accomplished by the use of two flashing lamps, marking fifths of seconds on each of the two records simultaneously. Occasional interruption of the signal circuit indicates a corresponding instant in the two records. From the first flash of the lamps following such an interruption, the events in each tracing may be accurately measured. An ink dot is placed at one signal on each record to indicate that these are synchronous points. In some instances, irregularities of the flash interval follow a period of interruption; these should not be mistaken for irregularities in paper speed.

plex lies on the descending limb of the T wave—usually on the latter part of the wave.

It is interesting that, in most cases, a well-defined wave occurs in early diastole; this corresponds to the point occupied by the normal third

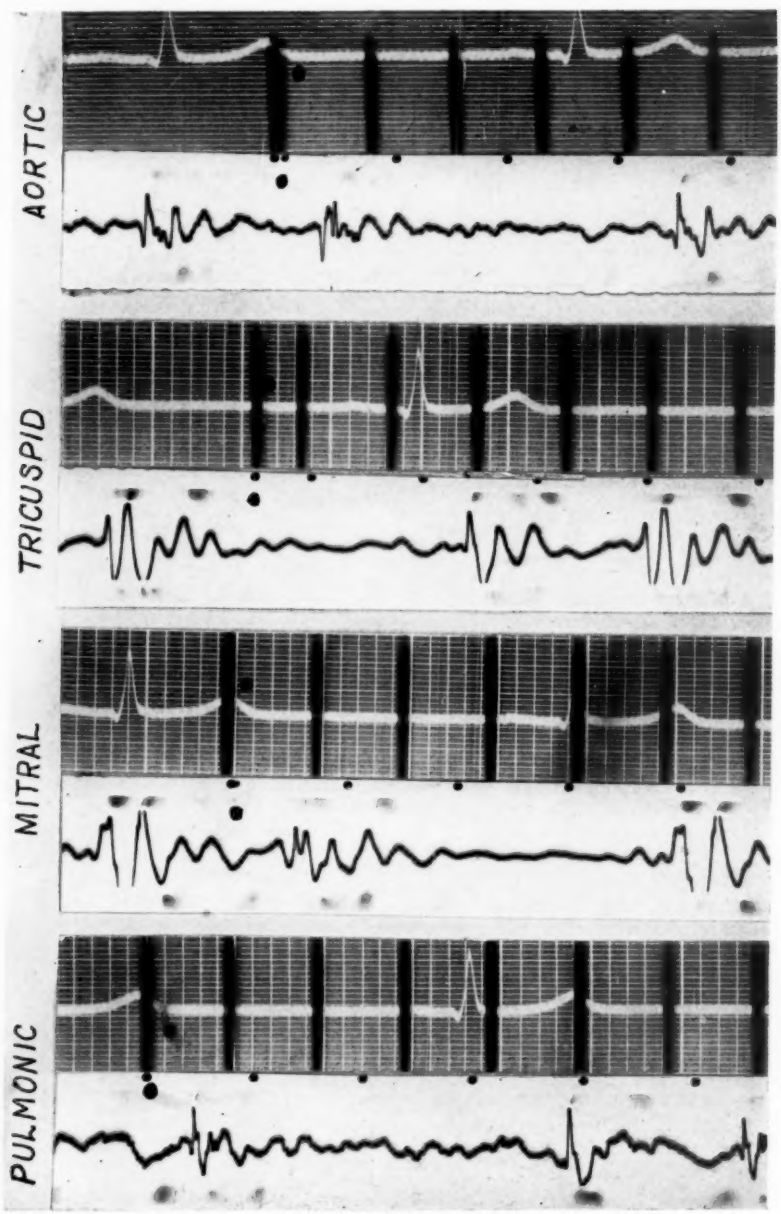

Fig. 3.—J. G., white man, aged 24 years. No history of cardiac or pulmonary disease.. Sthenic habitus; heart not enlarged. Normal heart sounds at all auscultation areas, although there is close splitting of second sounds at the pulmonic and aortic areas. Aortic second equals pulmonic second sound.

heart sound, although no third sound may be heard on auscultation. This wave is usually of low frequency and of no acoustic value. When such a wave is clearly present in the tracing from one auscultation area, it may generally be detected in any of the other three areas. McKee[12] noted, in studying stethographic tracings from 100 normal children, that four heart sounds were usually present; that is, in addition to the

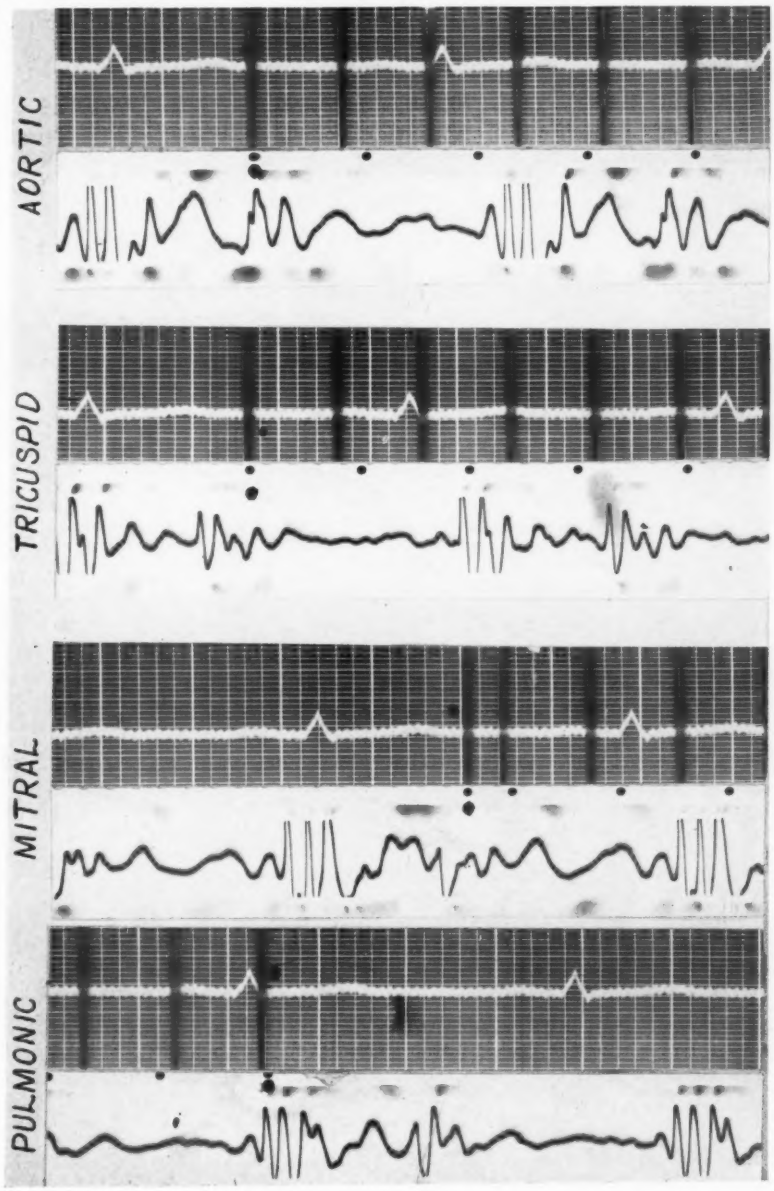

Fig. 4.—M. S., white man, aged 38 years. No history or physical signs of heart disease Hypersthenic habitus. The sounds are of "good quality" at all areas.

first and second sounds, a physiologic third sound wave occurred early in diastole, and a fourth sound wave, supposedly auricular in origin, preceded the first sound waves. In her series, 69 per cent of the tracings showed a third heart sound complex, and 94 per cent showed a presystolic sound. The "third" and "fourth" sound wave groups may

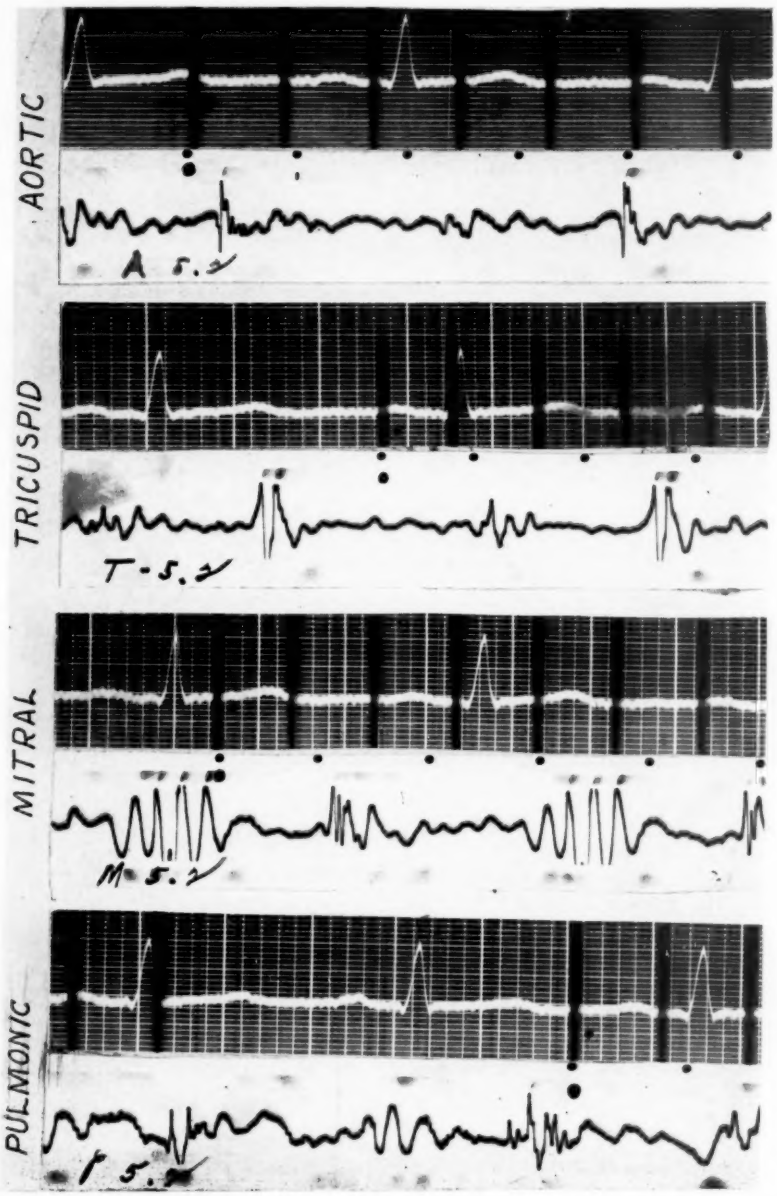

Fig. 5.—J. T., white man, aged 23 years. No signs of cardiac abnormality. Hyposthenic habitus. The heart sounds are of normal character at all areas. Note pronounced "auricular" waves in mitral area tracing.

be recognized in most of our records as well-defined waves of low frequency (below auditory level).

Duration of Vibrations.—The duration of the vibration complexes likewise varies with the area of the precordium from which the curve is recorded. At the aortic, tricuspid, mitral, and pulmonic areas, the first wave complex extends over a period ranging from 0.14 to 0.24 second. The presystolic waves which occur during the P-R interval, although they are of low frequency and without acoustic significance, must be considered a part of the disturbance incident to the atrial and presphygmic phases of the heart cycle. Therefore, these measurements include the envelopes which occur between the P wave and the point where they disappear, during the R-T interval, and comprise the "first wave complex." As a rule, the "second wave complex" is of shorter duration; it varies from 0.02 to 0.16 second. It should be emphasized that the first (audible) sound is, of course, normally of much shorter duration than the vibration complex described above, and that the vibration complexes are reflections of vibrations arising within the heart and of movements of the heart itself which are imparted to the chest wall during the cardiac cycle.

The instruments that have been previously devised for graphic registration of the heart sounds have usually been constructed so that sufficient distortion is introduced into the curves to minimize adventitious sounds or to emphasize various audible frequencies. This may only be accomplished, however, by sacrificing lower frequencies which, in themselves, may be inaudible or ill defined, but, when summated with other waves, help to establish the character of the sound. Furthermore, only a small segment of the disturbance is recorded, so that its exact relation to the cardiac cycle may not be well defined. The onset of the first sound has been located, by various observers, using different instruments, at the peak of the R wave or on the ascending or descending limb of the R wave. The use of the cathode-ray unit with these transmission characteristics shows, however, that the first heart sound complex begins during auricular systole; the character of these waves, as regards number and frequency, may possibly modify the audible qualities of the first sound. Such records may be of distinct advantage in detecting cardiac abnormalities that might otherwise be missed.

SUMMARY

An instrument which embodies a special dynamic microphone, amplifiers, and cathode-ray tubes, whereby vibrations set up by the heartbeat may be recorded, is described. Two cathode-ray tubes are employed; one is used to photograph the vibration complexes on a moving film, and the other, which has a long-persistence screen, is used as a viewing

tube. Curves obtained from normal hearts are presented. Certain advantages which this instrument seems to have over other stethographic devices are discussed.

The authors wish to express their appreciation to Lida W. Smith for financial assistance in this work.

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A MORPHOLOGIC STUDY OF THE CARDIAC CONDUCTION SYSTEM IN UNGULATES, DOG, AND MAN

Part II: The Purkinje System

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JOHANNES Evangelista Purkinje died in 1869. It is unfortunate that he could not have realized the important role which the Purkinje cells were to play in the development of modern cardiology. These peculiar muscle elements were first seen by Purkinje in sheep hearts, and described by his pupil, Palicki,[1] in 1839, and by himself[2] in 1845. They constitute a distinct type of muscle tissue (Fig. 1*A*) which can readily be distinguished from other myocardial elements. The cells occur in rows, two to five of which form a strand (Fig. 2*B*). The cells are short, thick cylinders, with distinct outlines (average diameter, 30 to 60 microns). The cytoplasm is slightly basophilic, the fibrils are irregularly arranged, and cross striations are rare and indistinct (Fig. 1*B*). The cells are characteristically binucleated (Fig. 2*A*). The nuclei lie at or near the clearer center of the cell; they are oval; their long axes often run transversely; and they contain a moderate amount of chromatin. Occasionally, only one nucleus is seen; less frequently, there are more than two. The cells are practically identical in structure and arrangement, wherever they are found. However, when the strands are compressed between muscle bands, they appear thinner and longer.

We have studied the Purkinje system in fifteen bovine, seventeen ovine, three equine, and five porcine hearts. Critical study of homologous areas in thirty-six human and seventeen canine hearts has led us to conclude that the structure of the so-called sinoventricular conduction system in these forms differs radically from that in the ungulate heart.

THE ORTHODOX VIEW OF CARDIAC CONDUCTION

According to the view held by most cardiologists and physiologists, the cardiac impulse is transmitted from the right auricle to the ventricles and spreads out over the inner myocardial surfaces of the ventricles through the Purkinje system. Most experimental cardiologists also hold that the secondary and tertiary impulse centers are found only in Purkinje elements. This conception of the conduction system of the heart developed from the work of Tawara,[3] Moenckeberg,[4] Lewis,[5] Mahaim,[6] Yater,[7] and others. It is essentially as follows:

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The Purkinje system is present in all higher animals (also in birds—Drennan[8]). In man and dog, as well as in other animals, it begins as ordinary or special auricular muscle fibers in the right auricular wall, in front of, below, and above, the coronary sinus. These auricular fibers run toward the central fibrous body, near which they change into a special type of muscle which forms the node of Tawara. The anterior fibers of the node run into the connective tissue of the central fibrous body, and become the essential constituent of the His bundle.

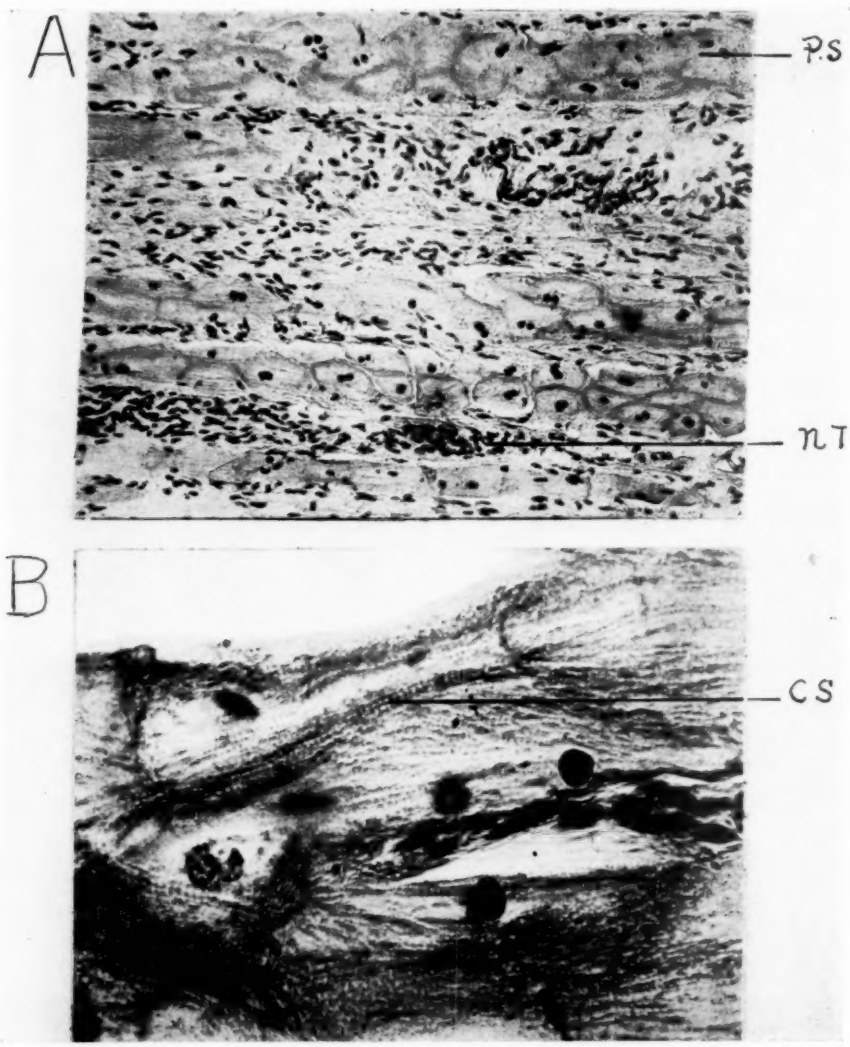

Fig. 1.—Purkinje fibers (bovine). *A:* From right bundle branch; *PS*, Purkinje strand; *NT*, nerve trunk. *B:* Purkinje cells (×1,000); *CS*, cross striations.

In man and dog, the left branch separates into fasciculi which are given off from the main trunk at different levels. These "soon" be-

come Purkinje fibers, which spread out over the inner surface of the ventricular myocardium. The right branch enters the myocardium below the tricuspid base, and runs within the myocardium to the papillary muscle. In the intramyocardial portion, the fibers of the branch are similar to ordinary myocardial fibers. At the level of the papillary muscle the branch becomes subendocardial, and its fibers change to Purkinje cells which spread out in strands underneath the endocardium.

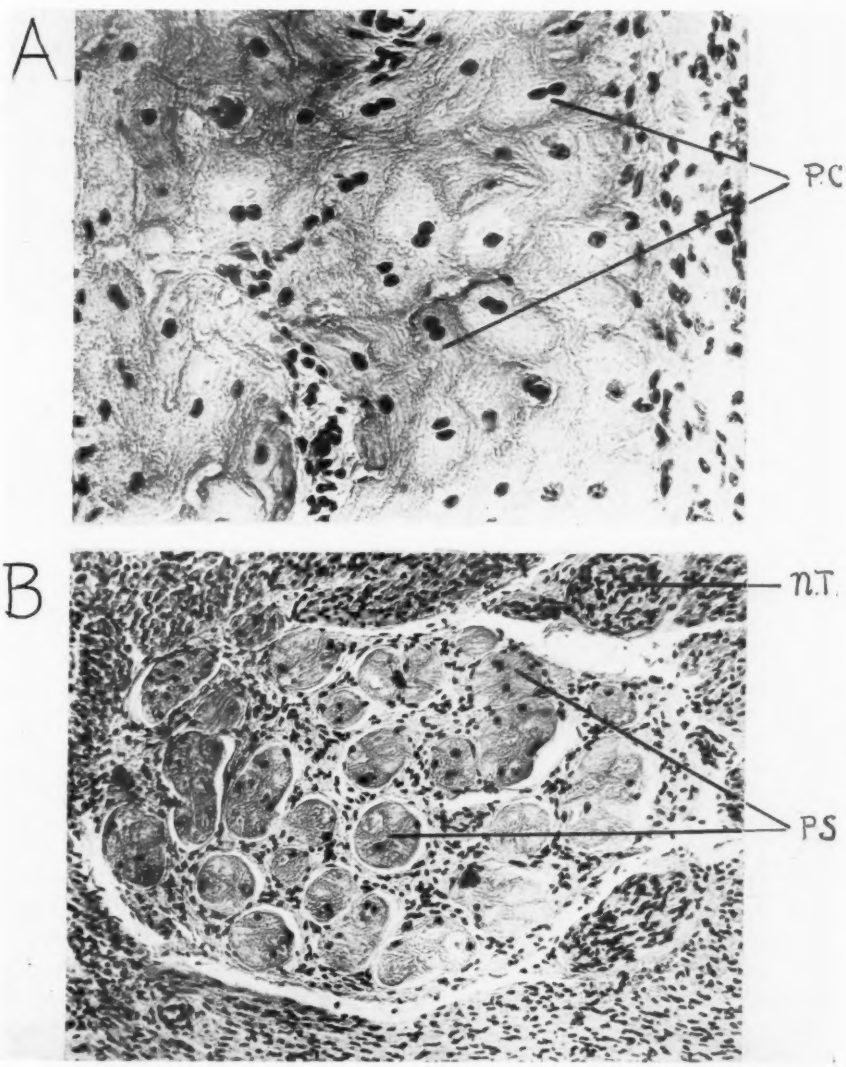

Fig. 2.—Purkinje cells (sheep). *A:* From Purkinje network; *PC*, Purkinje cells. *B:* Cross section of branch in moderator band; *NT*, nerve trunk; PS, Purkinje strands.

In the ungulate the main bundle bifurcates at the lowermost portion of the septum membranaceum, and each branch runs obliquely down-

ward through the myocardium toward the endocardial surface of the heart. The right branch becomes subendocardial at the base of the moderator band; the left, at various distances above the papillary muscles. Secondary branching occurs on both sides of the septum below the point where the branches become subendocardial, and from this branching a subendocardial network is formed. The essential constituent of the main trunk, its branches, and the subendocardial network is the Purkinje cell.

THE PURKINJE SYSTEM IN SHEEP AND CATTLE

In the bovine and ovine hearts which were used for this study, we found no direct muscular connections between the atrial muscle fibers and those of the node of Tawara. The node is best exposed by cutting the attachment of the lateral, right auricular wall to the fibrous auriculoventricular ring, and then severing the attachment of the atrial muscle to the septal base of the tricuspid valve. The atrial wall can then be readily lifted up and to the left, thus exposing the areolar tissue in the auriculoventricular groove. This tissue separates the lower, posterior, right atrial wall from the right, upper, ventricular septum, and, when it is removed, the node of Tawara comes into view.

I. THE NODE OF TAWARA

This muscular nodal tissue has its origin in the posterior right part of the central fibrous body and lies in the areolar tissue at the top of the muscular ventricular septum. In sheep it is usually knob-shaped. In cattle it is, as a rule, fan-shaped (Fig. 3). The "fan" handle forms the attachment to the central fibrous body and the beginning of the bundle. The node is faintly yellow, and its upper surface looks like a heap of matted yarn. Its peripheral tissue sprawls out over the top of the ventricular septum to the right and downward. A prominent strand which forms the upper limit of the node runs backward along the central fibrous ring. The anterior boundary is often made up of another heavy strand which runs downward into the right ventricle. Between these two strands, groups of fibers meander out from the middle of the node. Near the central fibrous body these interlace to form a network; more laterally, they are lost in the fatty tissue of the auriculoventricular groove. Some of the basal fasciculi of the node run forward and become the Purkinje elements of the His bundle.

The histologic structure of the node was accurately and lucidly described by Tawara. The nodal parenchyma consists of a mass of faintly cross-striated, slender muscle fibers, which either interlace or form whorls (Fig. 4*A* and *B*). The diameter of the individual fibers is slightly less than that of the average atrial and ventricular muscle element, and the fibers seem to possess more nuclei. These are usually rod-shaped or oval. In the whorls, diplonuclei, characteristic of Purkinje cells, are seen. The meshes of the reticula vary in shape and in

size. They are largest in the peripheral part of the node. The strands that make up a reticulum are composed of many layers of closely packed cells. The reticulated arrangement is most marked in the strand of nodal tissue which extends into the ventricle. The whorls are most numerous in the upper strand. In the whorls, cell outlines are fre-

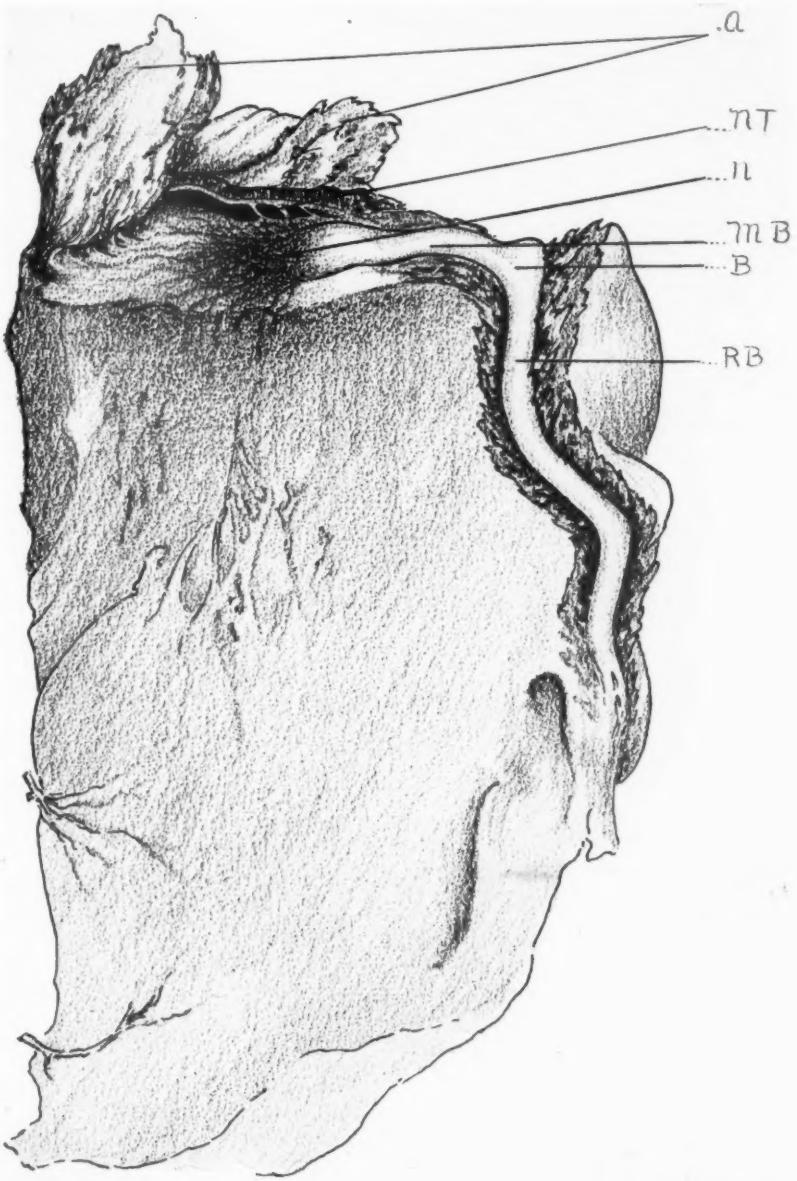

Fig. 3.—The His bundle (bovine). *A*, Auricular wall (turned back); *NT*, nerve trunk; *N*, node of Tawara; *MB*, main bundle; *B*, bifurcation; *RB*, right branch.

quently absent. We have never observed vessels larger than arterioles, and capillaries are scarce. Nerve elements are present near the His bundle and also in the peripheral part of the node. The meshes of the reticula are filled with loose, connective tissue.

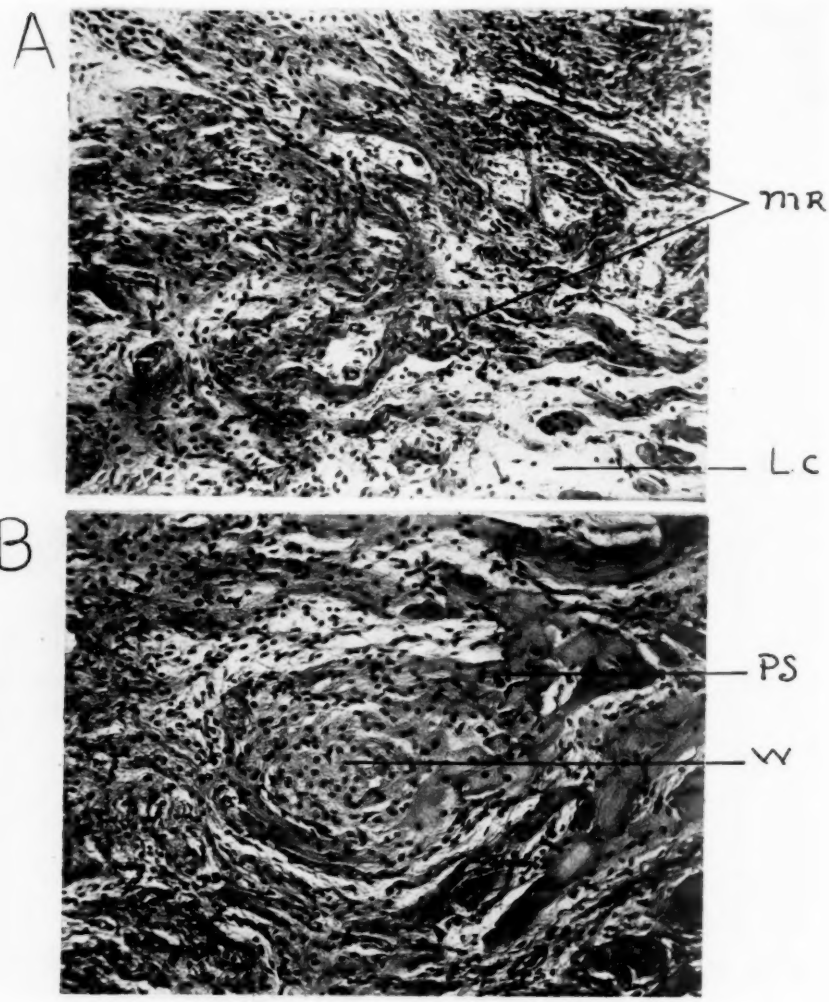

Fig. 4.—The node of Tawara (sheep). *A: MR*, muscular reticulum; *LC*, loose connective tissue. *B:* Beginning of His bundle; *PS*, Purkinje strands; *W*, whorl.

II. THE HIS BUNDLE AND PURKINJE NETWORK

A: Gross Description

In sheep and cattle the His bundle and the Purkinje network are practically identical except as to size. The trunk, beginning to the right of the central fibrous body, runs forward and downward at the top of the muscular ventricular septum. At the lowest part of the fibrous septum, it divides into a right and a left branch. These make their

way through the myocardium obliquely, to the endocardium of their respective ventricles. The branches reach the inner lining of the heart just above the moderator band on the right side, and at various distances above the papillary muscles on the left. Secondary branching takes place on both sides as the endocardium is reached. On the right side small branches are given off at the base of the moderator band. The main branch, however, continues forward in the band, giving off numerous twigs within it, and, as the remainder of the branch reaches the anterior wall of the ventricle, it breaks up into numerous smaller twigs. The secondary branches form the right Purkinje network. On the left side, the branch forks, one limb going to the anterior, and the other to the posterior, papillary muscle. In the crotch between the limbs many small twigs are given off. By further subdivision of limbs and twigs the left Purkinje network is formed. The subendocardial Purkinje network can be seen with the naked eye in the hearts of sheep and cattle. And, because the His bundle and the Purkinje network are ensheathed in connective tissue, the space between the connective tissue and the Purkinje elements can be injected with a suspension of colored particles. DeWitt[9] had a beautiful model of the bundle and the Purkinje network constructed in 1909. Lhamon[10] injected the network with India ink, in 1912; Aagaard and Hall,[11] in 1914, and Cardwell and Abrahamson,[12] more recently, made similar injections.

B: Microscopic Description

The main bundle and the Purkinje network are composed of strands of Purkinje fibers and collections of nerve fibers. These are separated by interstitial tissue and surrounded by a sheath of connective tissue. In the upper, anterior part of the node of Tawara, some of its muscle strands change abruptly into characteristic Purkinje cells. These, together with the nerve trunks which join them at this place, form the main part of the His bundle. The Purkinje strands rarely interlace in the bundle but run in a more or less parallel fashion among the nerve trunks. The strands continue through the right and left branches and into the Purkinje network.

It is generally assumed that the Purkinje strands terminate by changing into ordinary ventricular muscle near the endocardial surface, but Hessling,[13] as early as 1854, found Purkinje fibers intramuscularly and subpericardially. Cardwell and Abrahamson followed the Purkinje strands far into the myocardium of both ventricles, and found them just underneath the pericardium and penetrating the entire septum. We found Purkinje strands deep in the muscle of the septum, on the right and left sides, and within a millimeter of the pericardium of both ventricles. Thus, the Purkinje strands form an intramyocardial as well as a subendocardial network. Nowhere did we find any histologic evidence of a change from Purkinje cell to ordinary muscle fiber. Even the thinnest Purkinje strand is separated from the myocardium by connective tissue.

Such, in brief, are the structure and the arrangement of the Purkinje cells in sheep and cattle. These elements constitute only a part of the His-Tawara system. The Purkinje strand is neither the most conspicuous element, nor, perhaps, the most important part of the His bundle. Although Wilson,[14] as early as 1909, accurately described the nerve tissue of the part of the His-Tawara system which he had investigated, it is astounding that investigators of the His bundle should have given such scant consideration to its nerve elements. Attention has been called to the fact that nerve elements occur in the anterior part of the node of Tawara. Numerous nerve trunks and large blood vessels occur in the fascia at the top of the muscular septum, and many ganglion cells and nerves are found in the auriculoventricular groove in the periphery of the node. In the areolar tissue surrounding the main bundle, numerous ganglion cells and nerve fibers occur. In places these form groups containing hundreds of nerve cells (Fig. 5*A*). Wilson observed large collections of these cells at the bifurcation of the bundle; we found them there, and also in the periphery of both main branches (Fig. 5*B*). In the trunk and its right and left branches, nerve fibers occupy more than half of the structure. Nerve fibrils accompany every Purkinje strand.

Thus, there exists in these ungulate hearts a peculiar type of muscle tissue which differs strikingly from that of other cardiac muscle elements, both in structure and arrangement. This tissue is located in the ventricles, appears to originate in the central fibrous body, forms the node of Tawara and the Purkinje strands of the His bundle, and spreads out as a network, not only underneath the endocardium, but also intramuscularly. The bundle also contains numerous nerve fibers and ganglion cells, and nerve fibers accompany the Purkinje strands in the Purkinje network. The entire system is supplied with capillaries, minute arteries, and veins, and is separated by connective tissue from the rest of the heart.

THE PURKINJE SYSTEM IN THE HOG

The Purkinje system in some porcine species is very similar to that in sheep and cattle. In other species, in which the moderator band and the papillary muscles are poorly developed, the Purkinje system is inconspicuous. As a rule, the node lies nearer the tricuspid base than in sheep and cattle. The nodal tissue appears to be plastered to the upper part of the right side of the interventricular septum. In some hearts a band of nodal tissue extends backward to the right of the central fibrous ring. In the hog, as in the other species studied, a conspicuous septal branch of the right coronary artery, which travels subpericardially in the auricular wall toward the central fibrous body, leaves the atrial wall and enters the ventricular septum just posterior to the central fibrous body. This is the artery which has been designated by other observers as the artery of the node. The septal artery followed this course in only 20 to 30 per cent of the hearts which we studied.

The main bundle and the right and left branches, as well as the Purkinje network, are indistinguishable from homologous parts in sheep and cattle. The histologic structure is also nearly identical, except that the interlacing in the nodal part is not so apparent; the nodal musculature simulates the Purkinje cells much more than it does in sheep and cattle, and there is no abrupt change from the nodal cells to those of the bundle. Nerve bundles are more numerous in the hog, and the Purkinje cells are not so uniformly binucleated. An intramyocardial Purkinje network is also present in the hog.

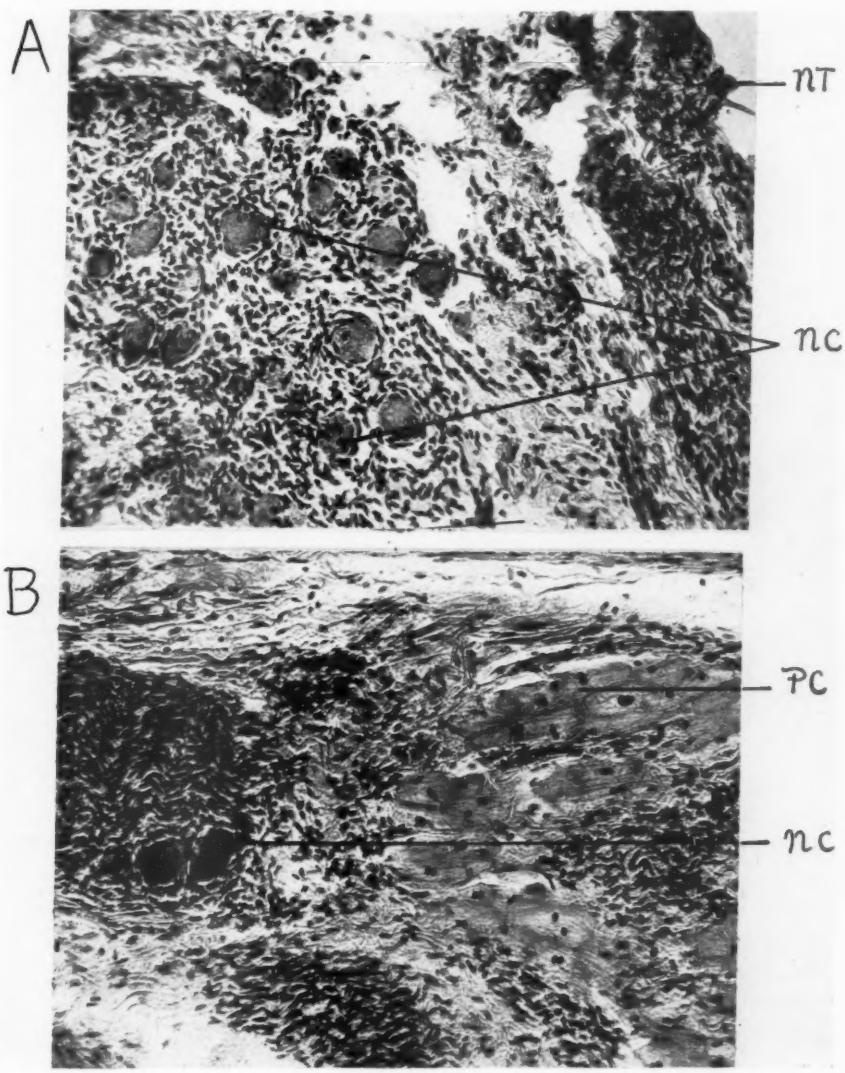

Fig. 5.—Nerve tissue in His bundle (bovine). *A:* Ganglion cells and nerve trunk (beginning of bundle); *NT*, nerve trunk; *NC*, nerve cells. *B:* Large nerve and ganglion cell (right branch); *PC*, Purkinje cells; *NC*, nerve cells.

THE PURKINJE SYSTEM IN THE HORSE

We were surprised to find that neither the node of Tawara nor the main His bundle could be brought to view in the equine heart by our dissection method, but, by removing the endocardium at the base of the small, fibrotic moderator band on the right side, and above the small, fibrotic papillary muscles on the left side, the thin, fibrous, right and left branches could easily be followed upward.

On the right side, the branch enters the myocardium, runs upward one to two millimeters underneath the endocardium, continues under the base of the tricuspid, and finally is lost in a tough fascia at the top of the right side of the ventricular septum in the locality of the septum fibrosum. Numerous bands of ordinary muscle fibers are attached to the branch. When these are picked off, the slender, ribbon-like branch is seen to be about two millimeters in width and less than one-half millimeter in thickness. On the left side, the tiny strands, running from each papillary muscle, unite to form the left branch in the region where the homologous junction occurs in sheep and cattle. The branch plunges into the myocardium, continues obliquely upward through the septum, and, finally, as a slender string about 1 mm. in diameter, enters the left side of the thick fascia, whence, like the right branch, it cannot be traced farther. Numerous muscle fasciculi are also attached to the left branch. Small branches of the ribbon appear to run into the myocardial septum. The left ribbon is wider and thinner than the right.

Histologically, the moderator band and the right branch are composed of fibrous tissue in which a few rows of distorted, misshapen, Purkinje cells are scattered. These appear atrophic. Many of the cells are without nuclei and only rarely is a diplonucleated cell seen. The left branch has the same structure as the right. In the connective tissue one small nerve trunk was seen. In cross sections taken from below the moderator band, a layer of large vacuolated cells, more or less surrounded by typical fat cells, is found subendocardially (Fig. 6*A*). Occasionally, strands of round, slightly basophilic cells, surrounded by a distinct layer of connective tissue, are encountered. These appear to be the Purkinje fibers, although nuclei are scarce. The thick fascia above the attachment of the tricuspid is made up of cellular, fibrous tissue in which are imbedded a single nerve and a few strands of shrunken Purkinje cells similar to those in the right and left branches (Fig. 6*B*). No definite node of Tawara was observed.

The thin ribbons encountered in the equine heart in the region of the right and left branches of the His bundle, and the strands observed in the fascia above the base of the tricuspid valve appear to be the vestigial homologue of the Purkinje system in sheep and cattle.

THE PURKINJE SYSTEM IN MAN

Gross Anatomy

Our experience in two cases of bundle branch block led to our interest in the conduction system of the heart. Post-mortem examination

revealed no significant lesions in the region of the left or right branch in either heart; therefore, we concluded that the proper localities had not been examined and determined to find the His bundle and its main branches by dissection. Since the His bundle is described and illustrated in texts on human anatomy (Spalteholz[15]), dissection of the bundle seemed feasible. When the first four or five dissections resulted in failure, the results were blamed on poor technique, but when the eighth, ninth, and tenth attempts were also unsuccessful, we began to question the statements and illustrations in the texts. By the time the fifteenth dissection of the bundle region in human hearts had been completed, we

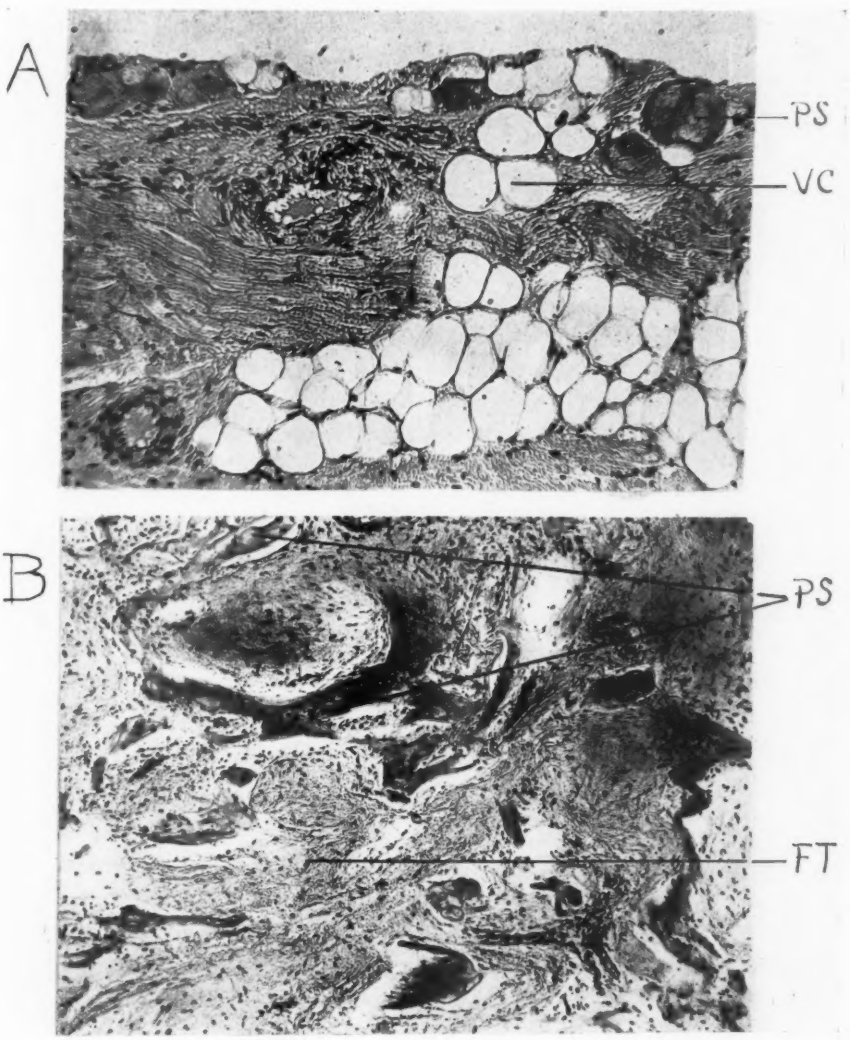

Fig. 6.—Purkinje cells (equine). *A:* Subendocardial Purkinje strand and fat cells (×110); *VC,* vacuolated cells; *PS,* Purkinje strand. *B:* Main His bundle (×90); *PS,* Purkinje strands; *FT,* fibrous tissue.

had read, in Mahaim's monograph, that gross dissection of the His bundle in man is impossible. Now, after having carefully studied the regions of the auriculoventricular node and the bundle of His in more than forty human hearts, we are quite ready to agree with Mahaim. A "special" conduction bundle cannot be found by gross dissection in the human heart. And we wish to add that the Purkinje system of the ungulate does not exist in man. However, the tissue which Mahaim and others describe as the bundle of His can be exposed by gross dissection. It is possible, without damaging the underlying muscular septum, to remove, bit by bit, the membranous septum, the connective tissue which forms the septal base for the tricuspid valve, and even the central fibrous body. When such a dissection is carried out, one finds that the upper ridge of the muscular septum is composed, in man, of a slender bundle of muscle fibers one millimeter or more in diameter. This forms the top of the ridge and runs into a canal in the central fibrous body. The lower part of this fasciculus continues underneath the base of the tricuspid valve, close to the septum membranaceum, runs subendocardially for a few millimeters, and then enters the muscular septum. Here the fibers spread out among the other myocardial elements. We have followed the slender strands into which this bundle divides for distances of five to ten millimeters in various directions in the myocardium and have found that they terminate like other subendocardial bundles. The "ridge" fasciculus is separated from the rest of the musculature by the same amount of interstitial tissue that is found elsewhere in the heart.

It is difficult to remove all of the fibrous tissue at the root of the aorta; but, when this is accomplished, and the endocardium is dissected away, the small fasciculi which Mahaim describes as the left branch can be seen distinctly and traced from their origin in the fibrous ring. Similar fasciculi are given off on the left side, not only in the region of the septum membranaceum, but also anterior and posterior to it. The strands where the bundle is supposed to bifurcate look exactly like those in front and behind it. Through the endocardium one sees frequently what appears to be the left branch of the His bundle. The "branch" seems to send one twig to the anterior, and one to the posterior, papillary muscle; but when the endocardium is removed, the illusion disappears, for the individual fibers which constitute this fasciculus are components of the septal muscle, which, after running a shorter or longer distance, terminate in the endocardium.

THE PURKINJE SYSTEM IN THE DOG

Gross Anatomy

Most of the experimental work on cardiac conduction in mammals has been carried out on the dog, on the assumption that a special conduction system exists in this animal, and that such a system consists of a sinoauricular node, an auriculoventricular node, and the bundle of His, with its ramifications. We have already reported our skepticism

concerning the existence of any specific conduction tissue in the sulcus terminalis of man, dog, sheep, cattle, horse, and hog (Glomset and Glomset[16]). Having failed to find, in man, a His-Tawara system of the type present in sheep and cattle, we searched for it in the dog. Fifteen canine hearts were dissected by the technique employed in our study of ungulate and human hearts. The muscle fasciculus which forms the upper part of the ventricular septum in the dog is strikingly similar to that in man. In this species, too, we believe that it is composed of ordinary muscle elements. It has been assumed that the visible fasciculus which runs from the base of the aortic valve toward the papillary muscles in the left ventricle is the left branch of the bundle. The dissection of the first canine heart convinced us that such is not the case, for this strand consists in the dog, as in man, of muscle fibers which have their origin at the base of the aortic valve. Subsequent careful histologic study of these fibers left us of the opinion that they differ in no essential feature from typical cardiac muscle.

MICROSCOPIC STRUCTURE OF THE HIS-TAWARA SYSTEM IN MAN AND DOG

A preliminary histologic survey of human and canine hearts convinced us that their so-called His-Tawara system differed radically from that found in sheep and cattle. Therefore, it became necessary to learn the histologic criteria used by other investigators. Prior to the year 1900, many investigators, including Purkinje, had failed to find Purkinje cells in human hearts, but, during the last three decades, the conviction that a special conduction system, containing Purkinje cells, exists in all higher animals has become fixed in the minds of cardiologists and physiologists. The various parts of the system are supposed to be found in the same localities in the dog and man as in the ungulates, and the form and structure are stated to be practically identical in canine and human hearts; but the histologic structure in man and dog is said to be different from that in sheep and cattle—so different, in fact, that only the trained eye of one who is continuously engaged in such studies can recognize and follow its ramifications (Winterberg[17]). Even such a person must study thousands of serial sections, and the loss of a single section may result in overlooking an essential lesion, or in losing the branch which is being followed (Mahaim).

In spite of the discouraging impression obtained from the literature, we decided to carry on, choosing for our differential criteria the descriptions of the microscopic structure of the His-Tawara system given by Tawara, Moenckeberg, Lewis, Mahaim, and Yater.

Table I epitomizes the conception held by these distinguished investigators of the minute anatomy of the conduction system in man and dog. A summary of the table follows:

The structure of the auriculoventricular node is not essentially different from that of the hoofed animals. It is smaller, the meshes are compressed, and a good-sized artery runs through it. (Mahaim's photo-

TABLE I

STRUCTURE OF HIS-TAWARA SYSTEM IN DOG AND MAN

		TAWARA, 1906	MOENCKEBERG, 1908	LEWIS, 1925	MAHAIM, 1931	YATER, 1938
Node of Tawara	Fiber mass	*Dog.* (Man—reticulum, less marked; meshes compressed.) Forms dense network; narrow, rounded meshes.	*Man.* Forms reticulum.	*Dog.* Man, similar to dog. Intricate interlacing; fibers cross and join at all angles.	*Man.* Macro: Ovoid, fan-like, imbedded in fat. Micro: Forms reticulum with wide meshes.	*Man.* Compared with Sinoauricular node. Reticulum, similar to S-A node; whorls; not so compact; less connective tissue.
	Individual	Slender, pale-staining; striations indistinct.	Compared with auricular fibers: Paler, vesiculated; striations: fewer, less distinct.	Slender, spindle-shaped.	Slender, pale-staining.	Thicker than in S-A node; striations more frequently visible.
	Nucleus	1, 2, rarely 3; round, oval, spindle-shaped.	More, larger, less chromatin.			
	Connections	Direct with auricular fibers; gradual change to bundle.	Direct with auricular fibers in front, above, and below.	Abrupt transition from auricular fibers.	Direct connections to auricle; gradual change from auricle to node.	Fibers merge with auricular myocardium; invade central fibrous body; become bundle without definite line of demarcation.
	Connective tissue	Separates fibers.	Much. More in old persons.	Dense network, holds fibers apart.		Less than in S-A node.
	Blood vessels and nerves		Large artery and veins at times; many capillaries; no nerve elements.	Arteries conspicuous; nerve fibrils and ganglion cells, scattered profusely.	Nerve and large artery accompanying node. Several arteries cross node.	Large artery usually runs through node.

Main Bundle	Macroscopic	Prism-shaped; broader at bifurcation.		Ensheathed in isolated canal.	Cannot be dissected out.	
	Microscopic Fibers	Fasciculi: "more parallel" than in node.	Slightly larger than myocardial fibers; vary in caliber, pipestem like.	Compared with nodal fibers; stouter. "more parallel," increase in size to arborization.	At first forms thin uniform network (like Tawara's node); later "more parallel"; not so easily distinguished. Poor staining.	Larger, "more parallel" than nodal fibers; resemble more ventricular fibers (not so much myoplasm). No true connective sheath.
	Fibrils and striations	Numerous, irregular; form network with small "Knoten."	Few fibrils, peripherally.		Cross striations, rare.	
	Nuclei	Many; round, oval, spindle-shaped.	Size: same as myocardial. Small amount of chromatin.			
	Connective tissue	Surrounds fasciculi.	Surrounded by much connective tissue which sends septa into bundle.			No true connective tissue sheath.
	Artery Glycogen		Many capillaries and lymph spaces. No glycogen.	Glycogen present.	Artery accompanies bundle.	No main artery. Glycogen present.
Right Branch	Macroscopic	Narrow, cannot trace to termination.			Cannot be seen.	Whitish thread beneath endocardium.
	Microscopic	Similar to myocardial; fibrils parallel. Connective tissue separates fibers from ventricular muscle. Accompanied by branch from nerve trunk. Man similar to dog.	Fibrils parallel, compact, varying size, compared with ordinary muscle: difference in staining not marked, many nuclei: indistinct cross striations. Lower part enlarges, seen as yellow string; changes to Purkinje fibers which run subendocardially, contain glycogen.	Less distinct in human than in ungulate. Purkinje fibers present, rich in glycogen.	Thin fibers, similar to those of trunk of node, closely packed; soon look like myocardial fibers.	Closely resemble myocardial muscle; same size or larger; paler, parallel, closer together; not always distinctly separated from cardiac muscle. Runs into myocardium; emerges to spread out as Purkinje fibers near base of anterior papillary muscle—beyond which not recognized.

TABLE I—CONT'D

		TAWARA, 1906	MOENCKEBERG, 1908	LEWIS, 1925	MAHAIM, 1931	YATER, 1938
Left Branch	Macroscopic and microscopic	Rather broad at origin; farther on still broader, separating finally into several parts. Strings running in trabeculae, usually to both papillary muscles.	Given off as fasciculi, separated by connective tissue. At first, fibers are similar to bundle: pipe-like, hollow, with definite cross striations and few bridges. Undergo alterations of structure, finally becoming more like Purkinje fibers.	Purkinje fibers present, rich in glycogen.	Spread out fan-like, subendocardially; never resemble myocardial fibers. Soon become Purkinje fibers.	
Purkinje Cells	General	Subendocardial. Separated from rest of heart muscle by connective tissue.	Slightly different from ordinary heart muscle. Difference: variation in size of cell, more sarcoplasm, lighter staining; fibrils fewer, variation in size, lighter staining, different arrangement. Rarely change to ordinary muscle.	"Transition to muscle abrupt; done by decreasing size and increasing striations," Tawara. Communicates with ventricular myocardium.		Recognized, rarely on right side of septum; never on lower left side. Prominent in periphery.
	Microscopic	Short, broad sarcoplasm "territories" with definite borders; constricted in places.	Empty space in sarcoplasm near nucleus; some hollow, some solid. Constricting cross striations at irregular intervals.	Swollen. Striations sparse.	Large, irregular, of unequal caliber; show knobs; vacuolated.	Large, pale. Cross-striations readily observed.
	Fibrils	Few, complexly arranged. (More in man.)		Poor in fibrils.	Very few.	Peripheral and prominent.
	Nucleus		Many forms: spindle-shaped. Lie in space free from fibrils.	Large, pale, frequently multiple.		
	Glycogen		Present always.	Present.		

micrograph shows two vessels, but no conspicuous reticulum.) The nodal fibers change gradually into the main trunk of the bundle. Here the fibers run "more parallel," are more voluminous, and contain more striations, i.e., they become "more like ventricular muscle." In the intramuscular portion of the right branch, the cells are so nearly like ordinary ventricular muscle fibers that if one serial section is missing the branch may be lost! The left branch is given off at various levels, beginning one to two millimeters anterior to the node, in the form of strands that do not make a definite, compact branch. The fibers "soon" change into Purkinje strands. All Purkinje cells lie subendocardially, and may or may not be surrounded by connective tissue sheaths. None of the five authors mentions a subendocardial Purkinje network. The Purkinje cells are usually larger than ordinary muscle fibers, have a clear space around the nucleus or nuclei, and have indistinct striations and irregularly arranged fibrils. They contain glycogen, and change imperceptibly into ordinary muscle fibers. Nerve elements are mentioned as occurring only in the node (Lewis).

Purkinje did not find the cells he described in man or dog. Todd[18] describes two kinds of Purkinje cells in man—the embryonic and the adult. The embryonic cell is large and polyhedral; it has irregular fibrils and few striations. The adult cell is more like the ordinary heart muscle fiber. Both types are found throughout the entire myocardium, from base to apex. Van der Stricht and Todd[19] state that all heart muscle fibers probably develop from Purkinje cells.

It is evident, then, that, in man and dog, the His bundle, its branches, and their ramifications differ strikingly from the same structures in sheep and cattle.

PERSONAL OBSERVATIONS

We examined the bundle region histologically in thirteen human and twelve canine hearts. The fresh tissues were fixed either in Bouin's solution or in a 10 per cent solution of formalin. Many of the dog hearts, and some of the human, were fixed while still warm. Sections were stained with iron-hematoxylin, hematoxylin-eosin, or Van Gieson. Complete serial sections were not made. Sections from the nodal regions were cut longitudinally and transversely from blocks that contained auricular wall, the central fibrous body, and the underlying ventricular septum.

Neither in the human nor in the canine heart did we see any muscular structure that looked like the node of Tawara, as seen in the hearts of sheep and cattle. Fig. 7*B* shows a section from the nodal region in man. It contains two branches of the septal artery and ordinary auricular muscle fibers.

We have studied many cross and longitudinal sections from the upper, middle, and lower parts of the septal ridge already described. Fig. 7*A* is a cross section of the ridge in man, and Fig. 8, *A* and *B*, is a

cross section of the ridge in the dog. As far as we can ascertain, the ridge is composed of ordinary ventricular muscle fibers both in man and dog. The microscopic structure of the subendocardial septal fibers in the left ventricle is seen in Fig. 9, *A* and *B*. We maintain that they, too, are ordinary muscle fibers that have been altered slightly in size and shape by their environment.

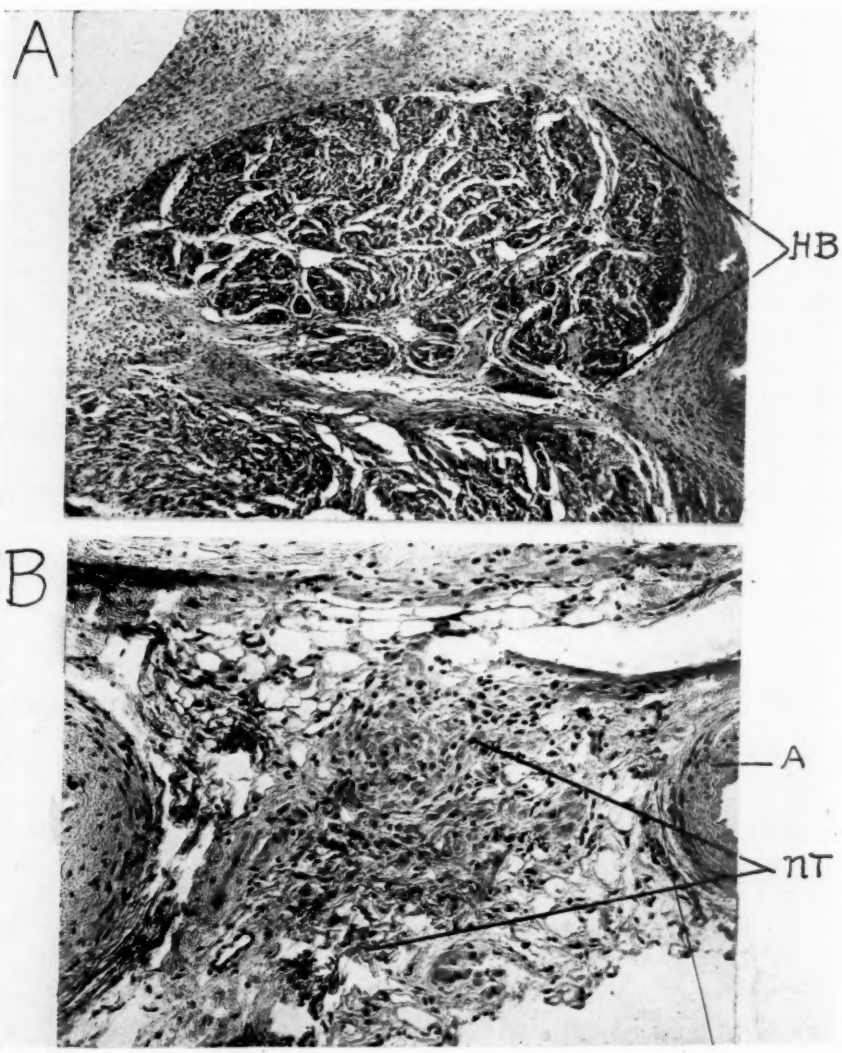

Fig. 7.—His bundle and A-V node (man). *A:* *HB*, "His bundle" (in canal of central fibrous body). *B:* *A*, artery of "A-V node"; *NT*, "Node of Tawara."

Cells which correspond to the description given for Purkinje fibers in man and dog and to the drawings of these cells by Tawara (Tafel V) are found under the endocardium in various parts of the ventricles. Such cells are often directly continuous with the ordinary myocardial

elements (Fig. 10*B*). Cells of this type are found occasionally under the pericardium and also in the deeper parts of the myocardium. They also occur in both right and left auricles. The "hollow" appearance of some of the "Purkinje cells," stressed by Moenckeberg, and the "vesicular" character, emphasized by other investigators, are probably artifacts, as suggested by Evans.[20] We have studied the region from

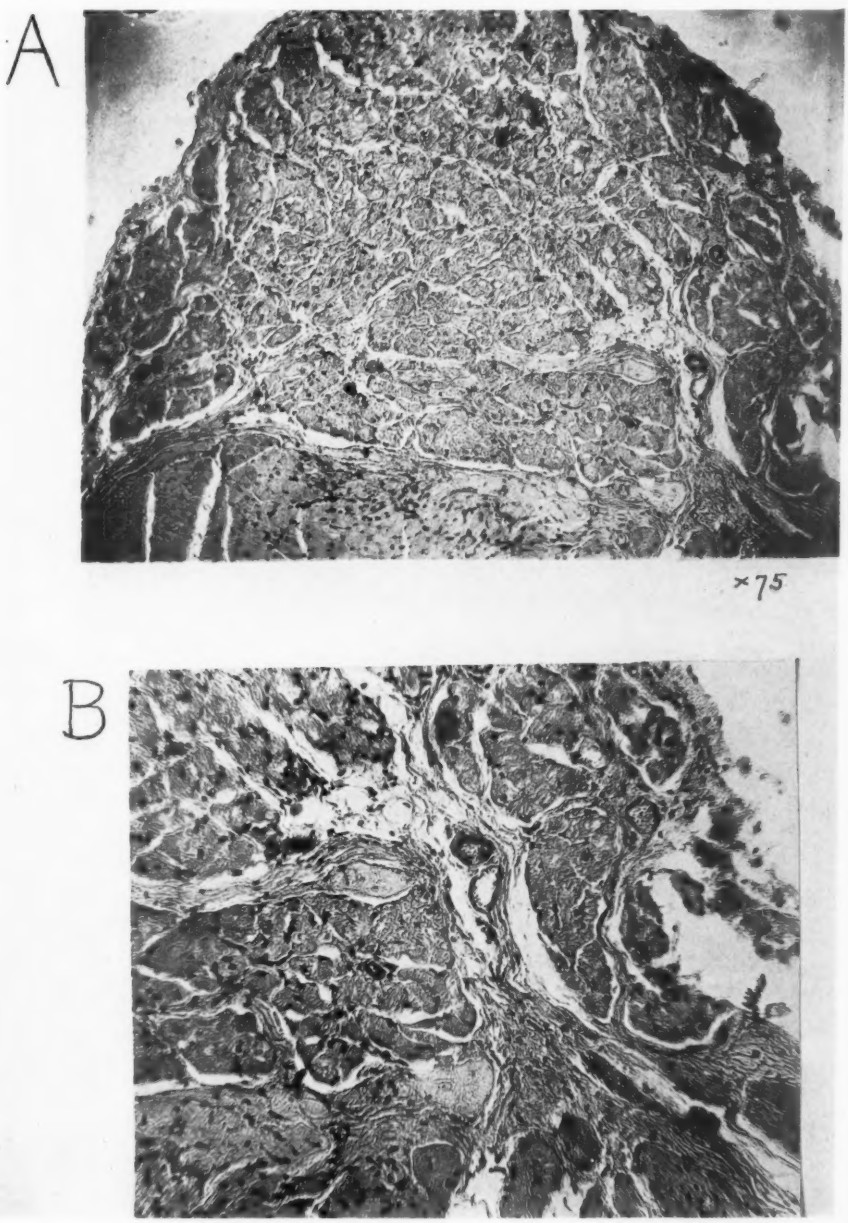

Fig. 8.—Muscular ridge of septum (canine). *A:* ×40. *B:* Part of *A* (×100).

which Wachstein[21] obtained muscle strips for his study of contractility and conductivity of the Purkinje fibers. Fig. 10*B*, from this region, shows that such strips must have been composed of ordinary muscle fibers. Similarly, we have studied the pseudo-tendons from the ventricles of the dog, which Ishihara and Nomura[22] claim are composed entirely of Purkinje fibers. These, too, we believe to be ordinary cardiac muscle fibers (Fig. 10*A*). All elements held by others to be Purkinje cells, in man and dog, are different from the true Purkinje cells found in ungulates.

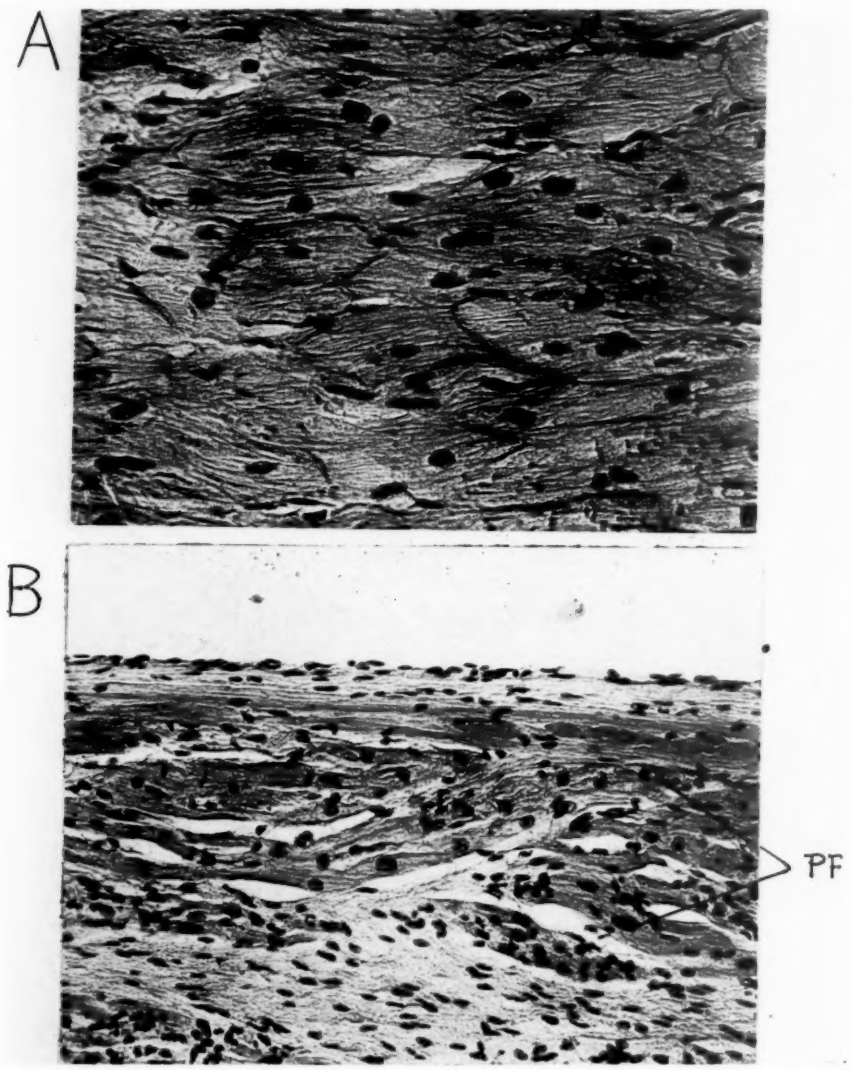

Fig. 9.—Cells from "bundle and left branch" (human). *A:* Muscle fibers of trunk (oblique). *B:* "Left branch"; *PF*, "Purkinje fibers."

Nerve tissue forms a conspicuous part of the conduction system in cattle, sheep, and swine. No mention is made of nerve elements in the structure described as the His-Tawara system in man and dog by the authors responsible for the information given in Table I, with the exception previously noted. Barton and Greenwood[23] and others found ganglion cells and nerve fibers in the nodal region in the dog heart. Our study disclosed both nerve cells and nerve fibers in this region. Nerves run in the atrial septum, and ganglion cells and bundles of nerves occur in front of, and behind, the central fibrous body in man and dog. These ganglion cells are a part of a wreath of nerve tissue which lies in the

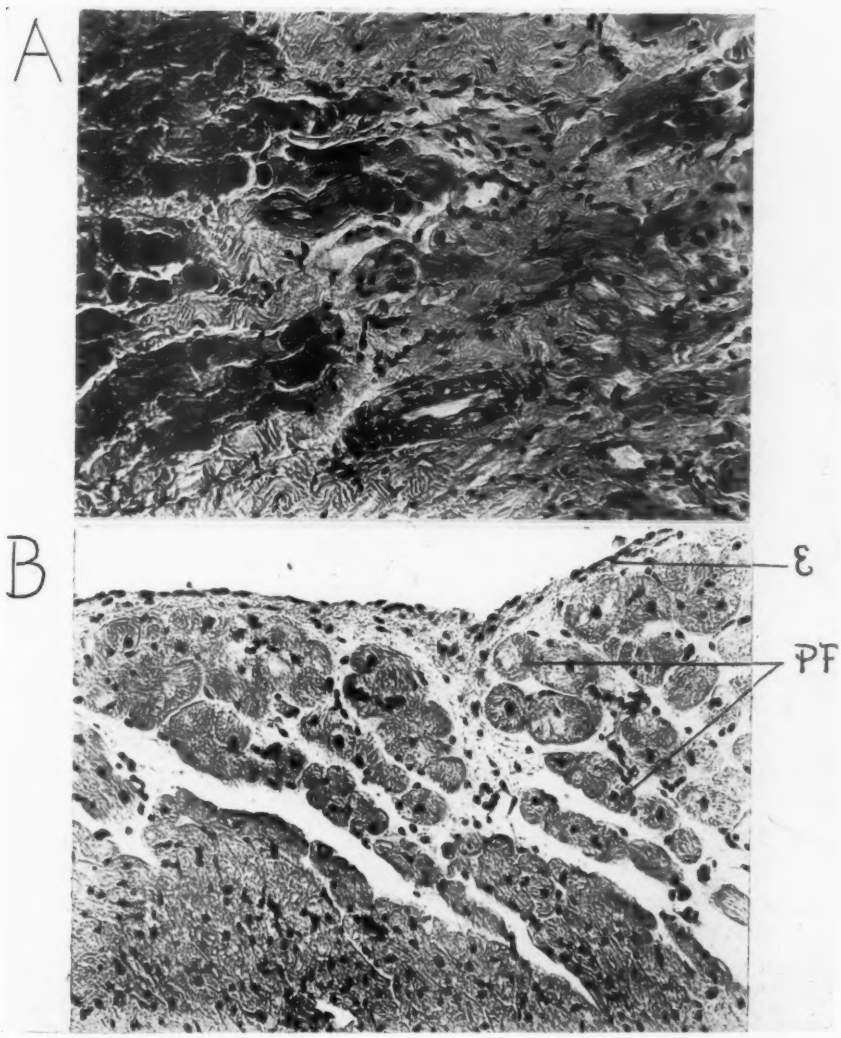

Fig. 10.—Purkinje fibers (canine). *A:* Section from pseudotendon. *B:* "Left branch," showing relation of "Purkinje fibers" to underlying myocardium; *E*, Endocardium; *PF*, "Purkinje fibers."

auriculoventricular groove. By special staining methods, Davies and Blair[24] demonstrated nerve twigs in what they took to be the His bundle and its branches in man. We found collections of nerve fibers throughout the myocardium of all of the cardiac chambers in man and dog; the nerve bundles, however, are smaller and fewer than in sheep and cattle.

GLYCOGEN

Marchand,[25] in 1886, observed glycogen granules in Purkinje cells. However, the idea that Purkinje fibers contain glycogen and that ordinary heart muscle does not appears to have originated in Aschoff's laboratory during the first decade of the present century (Aschoff and Nagayo[26]). Moenckeberg found glycogen in "Purkinje" cells, but none in the node of Tawara, the main bundle, or the right branch. Because of the prominence of the Aschoff group, their conception is widely known and generally accepted.

The present status of our knowledge concerning glycogen in Purkinje cells is excellently summarized in the article by Yater, Osterberg, and Hefke.[27] Glycogen can be detected in tissue by staining properly prepared sections with iodine or with Best's alkaline carmine, and the quantity of the substance present can be ascertained by chemical analysis. Histologically, glycogen has been demonstrated in the liver, skeletal muscle, Purkinje cells, tumors, and in ordinary cardiac muscle cells. Buadze and Wertheimer[28] found seven times as much glycogen in ordinary cardiac muscle as in the Purkinje cells of the horse. Yater, et al., found little difference between the glycogen content of ordinary heart muscle and the Purkinje fibers in the same animal, but great variation in individual hearts. Lewis[29] also noted that some artificially growing cardiac muscle cells contain glycogen granules, whereas others do not.

Our investigation of the glycogen content in tissue was limited to the study of sections stained with Best's carmine. Sections were examined from the anterior lower wall of the right ventricle of one sheep, from the same region and from the moderator band of a horse, and from the upper part of the septum of a two-hour-old baby. The tissues were submerged in absolute alcohol while they were still warm, and were imbedded in celloidin.

In the sheep, some Purkinje cells were "loaded" with red granules, and others contained none. In the horse, most of the Purkinje cells in the moderator band contained glycogen, and some of the large vacuolated polyhedral cells, lying subendocardially, were so crowded with granules that no cell structure could be seen. Others were free from the granules. In the septum from the baby, no large granules were found in any cell, but a faint pink stain was taken by most of the muscle elements. Both in the horse and in the sheep, small red granules were seen here and there in the endothelium of the endocardium, and also in the interstitial tissue.

From the information obtained in the literature, and from our own experience, we gain the impression that the presence of intracellular glycogen granules, as shown by staining with iodine or carmine, does not constitute a distinguishing feature of Purkinje cells.

COMMENTS

If one accepts the assertion that the structures described by the authors cited in the table constitute the special cardiac conduction system in man and dog, one is forced to concede that similar physiologic properties are possessed by tissues which are strikingly dissimilar morphologically, for the difference between the two nearly identical "His-Tawara systems" in dog and man, and the Purkinje system in ungulates, are many and significant. These are as follows:

1. A definite, easily recognizable structure, the node of Tawara, exists in cattle, sheep, and hogs. There is no such node in man or dog.

2. In sheep and cattle, the cells at the edge of this node change abruptly to strikingly different, binucleated Purkinje cells. These, without altering shape or structure, run in strands through the main bundle and its branches, form a subendocardial network, and penetrate the entire myocardium of both ventricles and the septum. In man and dog, however, it is admitted that Purkinje cells do not exist in the main bundle nor in the upper part of the right branch. The cells which are described as Purkinje elements in the left branch and lower right branch differ strikingly from those found in sheep and cattle. They do not form a network, are found only subendocardially, and have never been recognized within the myocardium.

3. In the upper part of the main bundle in sheep, cattle, and hogs, where nodal cells change into Purkinje elements, large numbers of nerve fibers enter the bundle. These form a conspicuous part of the main trunk and its branches; they also accompany the smaller strands. Ganglion cells are frequently found at the periphery of the main bundle and its right and left branch. Such nerve elements are found neither in the "bundle" nor in its subdivisions, in man or dog.

4. In sheep and cattle, the trunk, its branches, and their minute ramifications are surrounded by a distinct sheath of connective tissue. This permits visualization of the whole system after injection with suitable material. No such sheath is found in man or dog, and many attempts at injecting the system in these species have failed.

SUMMARY

Sheep, Cattle, and Swine

1. A distinct, ventricular Purkinje system has been found in sheep, cattle, and swine. This begins in a node which lies at the top of the ventricular muscular septum, near the posterior part of the central fibrous body in the right side of the heart. The fibers of this node do not have a direct connection with the auricular muscle fibers, but run in

strands which spread out over the posterior upper part of the ventricular septum, and even enter the right ventricle.

2. Only the anterior part of the node changes abruptly into the characteristic Purkinje cells, which run in strands through the bundle and its main branches, and form a subendocardial and intramuscular network in the ventricles.

3. Numerous nerve fibers and ganglion cells form a conspicuous and significant part of the His bundle and its ramifications.

4. The bundle, its branches, and the Purkinje network are surrounded by a sheath of connective tissue. Nowhere in the system have we seen the Purkinje cells change into ordinary ventricular musele.

Man, Dog, and Horse

5. In the horse a vestigial remnant of the Purkinje system is present.

6. In the dog and in man the local modifications of structure in the homologous positions do not appear to us to possess the characteristic features exhibited by the conduction systems of sheep and cattle.

7. Cells, in human and canine hearts, which are considered by others to be Purkinje elements, have been found in the atrial and ventricular musculature of the hearts of all of the species that we have studied.

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ELECTROCARDIOGRAPHIC CHANGES FOLLOWING METRAZOL-INDUCED CONVULSIONS

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DURING the treatment of psychotic patients with metrazol,* it has been reported by others,[1, 2, 3] and noted frequently by us, that immediately following the convulsion there is a pronounced, but temporary, cardiac arrhythmia. These observations together with the tremendous violence of the treatments, aroused our interest and led us to study the cardiac mechanism following metrazol-induced convulsions.

Electrocardiograms were taken on thirty-seven patients before and after forty-three convulsant doses and nine subconvulsant doses of metrazol. The three standard leads were taken just preceding the injection of the drug, and Lead II was again recorded immediately upon cessation of the convulsion, and at three, five, and ten minutes after the injection. Before the adoption of this procedure, it had been ascertained by taking tracings over a two-hour period that most of the significant changes occurred within the first ten minutes after injection of the drug. In some cases the patients became so violent that it was necessary to disconnect the galvanometer before the observations were complete. Whenever possible, the blood pressure was recorded simultaneously.

TABLE I

AGE DISTRIBUTION IN DECADES

Age in years	10-19	20-29	30-39	40-49	50-59	60-69
Number of cases	1	4	15	12	4	1

The patients' ages ranged from 19 to 65 years; the distribution by decades is shown in Table I. Sixteen of the patients were from private psychiatric practice, and the remaining twenty-one were inmates of a state institution. In all but five of the cases, which will be considered in detail later, the cardiovascular system was normal. Metrazol was used in a 10 per cent solution and was injected as rapidly as possible through an 18-gauge needle into one of the large veins of the antecubital fossa.

The major portion of this report deals with the changes which were observed when convulsant doses of the drug were administered. The effect of subconvulsant doses is discussed separately.

CHANGES IN BLOOD PRESSURE

Blood pressure measurements were made coincidentally with the electrocardiograms after thirty-one of the forty-three convulsions, and in all but two instances there was a sharp rise (Table II). The systolic pressure always rose more than the diastolic; the mean increases were 45 mm. Hg and 19 mm. Hg, respectively.

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*Metrazol (Cardiazol) is the proprietary name of pentamethylenetetrazol. It resembles camphor in many of its actions and is a strong convulsant and medullary stimulant.

TABLE II

CHANGES IN BLOOD PRESSURE

CASE NO.	CONTROL	IMMEDIATELY AFTER CONVULSION	3 MIN. AFTER INJECTION	5 MIN. AFTER INJECTION	10 MIN. AFTER INJECTION
2	120/80			170/100	132/82
3	135/80	180/110	200/130	160/100	135/90
5	170/110	210/100		190/90	150/70
6	160/90		190/90	160/70	
7	160/100	180/130	150/90	140/80	135/70
8	155/90	200/100	185/80		150/70
9	145/80	160/90	150/70	110/50	
11	155/90	210/100		170/90	140/85
13	140/90	180/100	150/80	150/80	150/80
14	145/80	170/100	165/100		120/70
15	140/90	135/70	135/60	120/60	
16	130/80		160/60	125/55	125/55
17	130/70	150/80		140/???	
20	140/90	195/90		170/100	140/80
20	150/90		200/110	160/70	135/70
23	150/90	185/100		185/90	160/90
24	150/90	190/100			130/85
25	120/80		130/80		110/70
26	130/85	185/120			
27	155/100	210/100		140/75	130/85
27	110/70	180/100	150/80		120/80
28	130/80	150/90	120/70		
29	150/94	150/90			
30	120/80	175/100	175/100	130/70	110/70
31	118/80	140/85	140/85	118/70	118/70
32	170/90	220/100	220/120		
33	120/80	195/100	168/100	140/75	140/75
33	110/70	170/90		140/90	110/70
34	210/110	300/120	250/120	220/90	220/90
35	100/70		140/80		
36	115/50	130/70	140/80	125/80	
37	160/100	150/110		200/120	140/90

Similar changes in blood pressure following metrazol convulsions in man have been reported by Hadorn,[2] and Forschbach,[3] and in animals by Müller.[4] These observations do not agree with those of Messinger and Moros;[1] we are unable to explain this fact, for their measurements were apparently made at approximately the same time after the convulsions.

CHANGES IN HEART RATE

Although variations in the cardiac rate were observed in all instances, there was no consistency in the direction or magnitude of these changes. If a change of twenty-five cycles per minute is arbitrarily assumed to be significant, cardiac slowing, cardiac acceleration, and no significant change in heart rate occurred with equal frequency. In a few instances the change in heart rate was conspicuous; in one, the rate fell from 136 to 38 per minute (Fig. 1*B*). The bradycardia was the result of temporary, complete A-V dissociation. In other instances the cardiac slowing was associated with inversion of the P deflections, indicating that the pacemaker had shifted to the A-V node. Sinus tachycardia occurred frequently; in one instance the heart rate rose to 160, and, in two others, to 176 and 177, respectively.

CHANGES IN RHYTHM

Gross cardiac arrhythmia was conspicuous immediately after all but eight of the forty-three convulsions. The disturbances in cardiac mechanism were of three types: those characterized by changes in the heart rate and location of the auricular pacemaker (Figs. 1 *A* and 2); those resulting from variations in A-V conduction (Fig. 1); and those caused by extrasystoles of various types (Fig. 3).

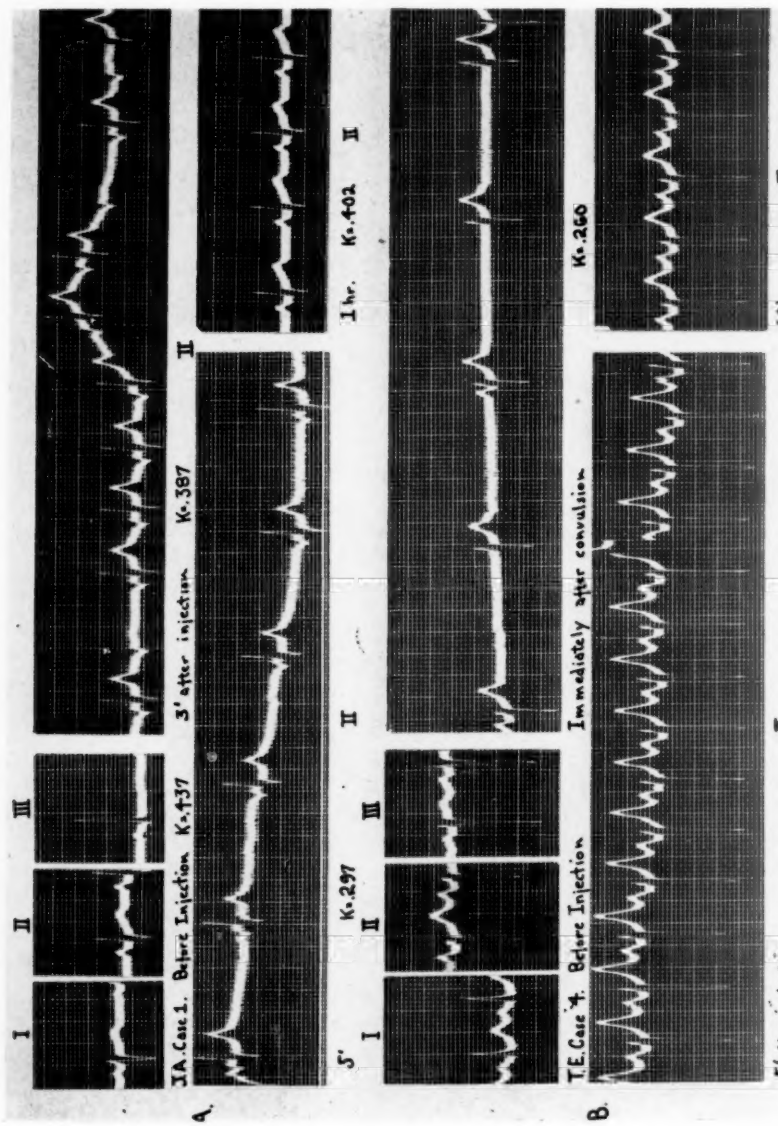

Fig. 1.—*A*, Case 1. A-V rhythm, with partial heart block, immediately following the convulsion. K is reduced, and there is a marked change in the contour of the T waves. *B*, Case 4. Complete A-V dissociation, with interference, immediately following convulsion. K is reduced, and there is a change in the T waves similar to that in *A*.

In some records only one of these disturbances was present, but more often two, or all three, of them occurred together. Table III indicates the various frequencies of each. Our records (Figs. 1, 2, and 3) are, for the most part, similar to those published by others.[2, 3] Although auricular fibrillation has been referred to frequently[2, 5, 6, 7] as a complication of the metrazol-induced convulsion, it was not observed in a

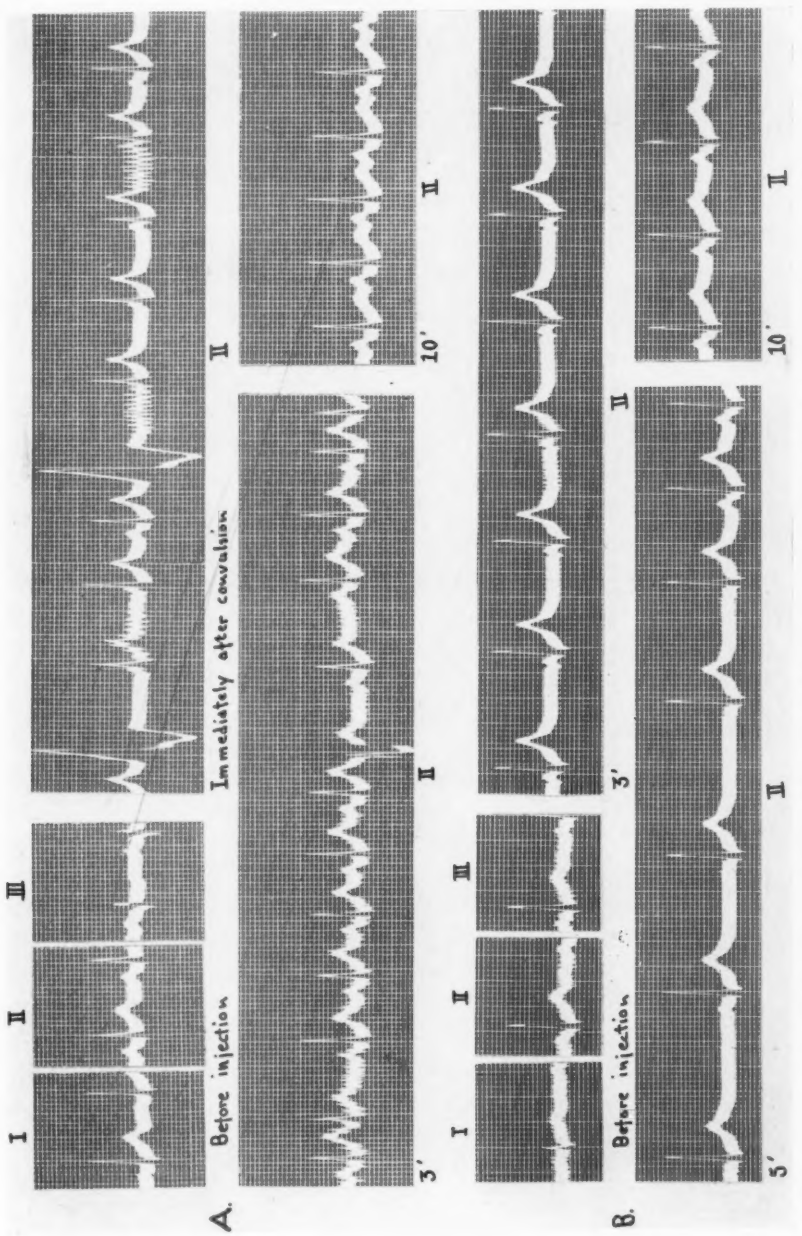

Fig. 2.—*A*. Case 5. Shifting pacemaker and ventricular extrasystoles immediately following convulsion. *B*. Case 11. A-V rhythm following convulsion.

TABLE III

TYPE AND FREQUENCY OF ARRHYTHMIAS

TYPE	NO.
Sinus arrhythmia (marked)	4
Shifting pacemaker	15
Atrioventricular rhythm	10
Prolonged P-R interval	3
Partial heart block	2
Complete A-V dissociation, with interference	2
Auricular extrasystoles (including one case of bigeminy)	19
Auricular extrasystoles (blocked)	1
Atrioventricular extrasystoles	4
Ventricular extrasystoles (including one case of bigeminy)	4
Number of convulsions following which the above observations were made	35
Number of convulsions following which no significant arrhythmia was observed	8
Total number of convulsions studied	43

single instance in this series. It should be pointed out that the great frequency of pronounced arrhythmias of other varieties makes the diagnosis of auricular fibrillation difficult, under the circumstances in question, unless an electrocardiogram is taken. Examination of our records clearly indicates the difficulty, if not the actual impossibility, of distinguishing clinically between these arrhythmias and auricular fibrillation. An electrocardiogram was taken in only one of the three cases of fibrillation reported by Dick and McAdam,[5] and this electrocardiogram was described as showing "partial flutter." Lubner[7] also reported a case of auricular fibrillation but made no mention of electrocardiographic confirmation.

The mechanisms responsible for the striking alterations in the rhythm of the heart which we observed are at the present time not definitely known. It seems probable that the changes in the location of the pacemaker were the result either of powerful vagal stimulation induced by the sudden increase in blood pressure, which occurred in most of the cases at approximately the same time, or of direct drug action. The disturbances in A-V conduction may be attributed to the same cause, or to anoxemia secondary to the convulsion. From our records, it was not possible to decide which of these factors was the more important, for both increased vagal tone and anoxemia depress the conductivity of the A-V node.[8] It should be noted that Erickson[9] and Hadron[2] did not observe cardiac arrhythmia in association with the spontaneous convulsions of epilepsy. The former states that the change in blood pressure during epileptic convulsions is extremely variable. To investigate further the cause of the cardiac arrhythmia in metrazol shock, it would have been desirable to repeat some of our observations after thorough atropinization, but under the circumstances of this study it was not possible to do this.

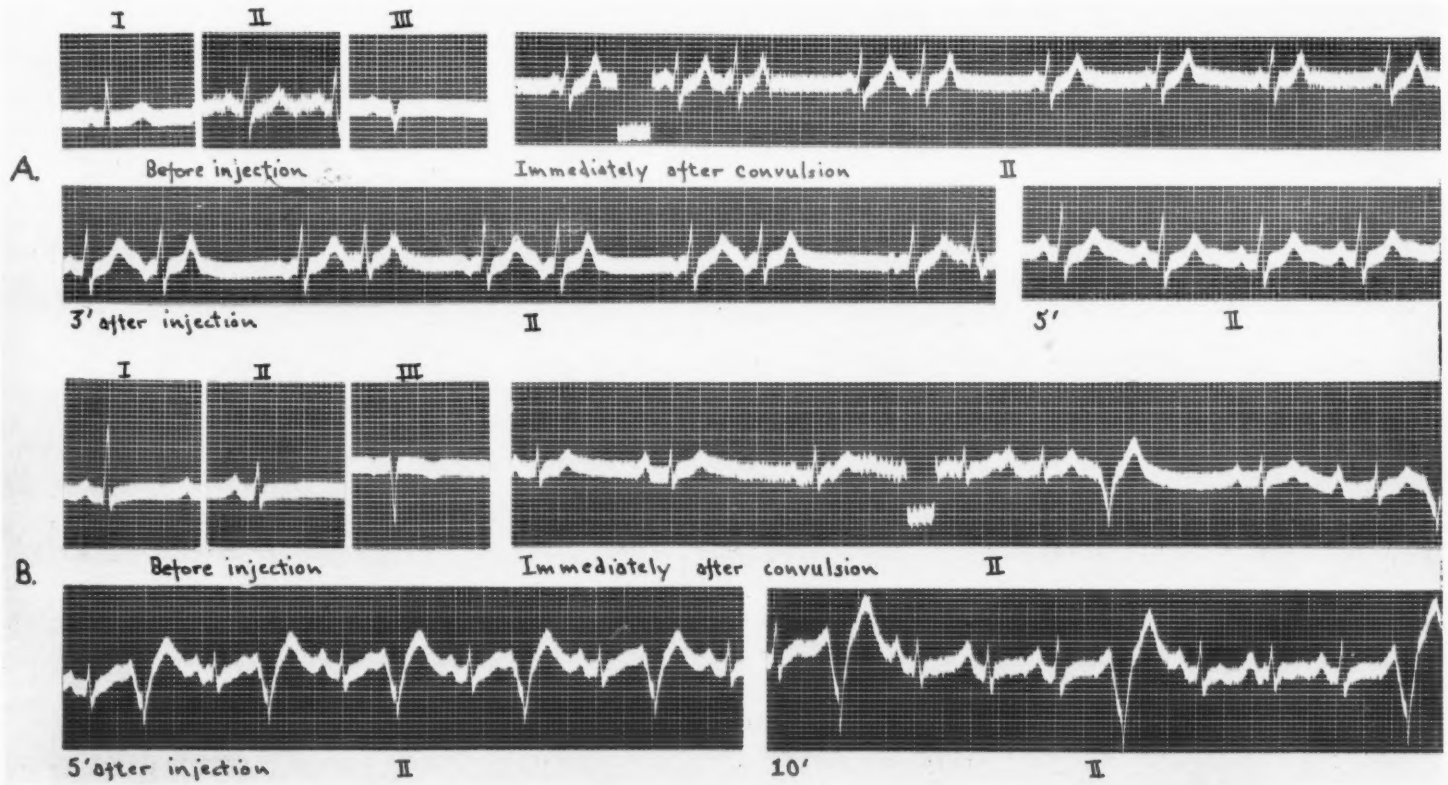

Fig. 3.—*A*. Case 29. Bigeminal rhythm produced by auricular extrasystoles. *B*. Case 37. Bigeminal and quadrigeminal rhythm produced by ventricular extrasystoles. T waves in Lead II became upright immediately following the convulsion.

CHANGES IN THE T WAVE

An increase in the amplitude of the T wave has been noted by others,[1] and occurred in the single lead which we recorded (Lead II) during thirty-three of the forty-three convulsions. This change was almost always most pronounced in the record which was taken immediately following the convulsion; in every instance the T wave had returned to its original amplitude by the end of the ten-minute period of observation. Although the increase in the height of T was usually no more than 1-2 mm., it was occasionally much greater. In Case 4 (Fig. 1 *B*), the height of the T wave increased from 5 mm. in the control record to 10 mm. in the record which was taken five minutes after the injection of metrazol. In two instances (Fig. 3 *B* and Case 34, Fig. 4), T waves which had been negative in Lead II in the control curve became positive following the convulsion.

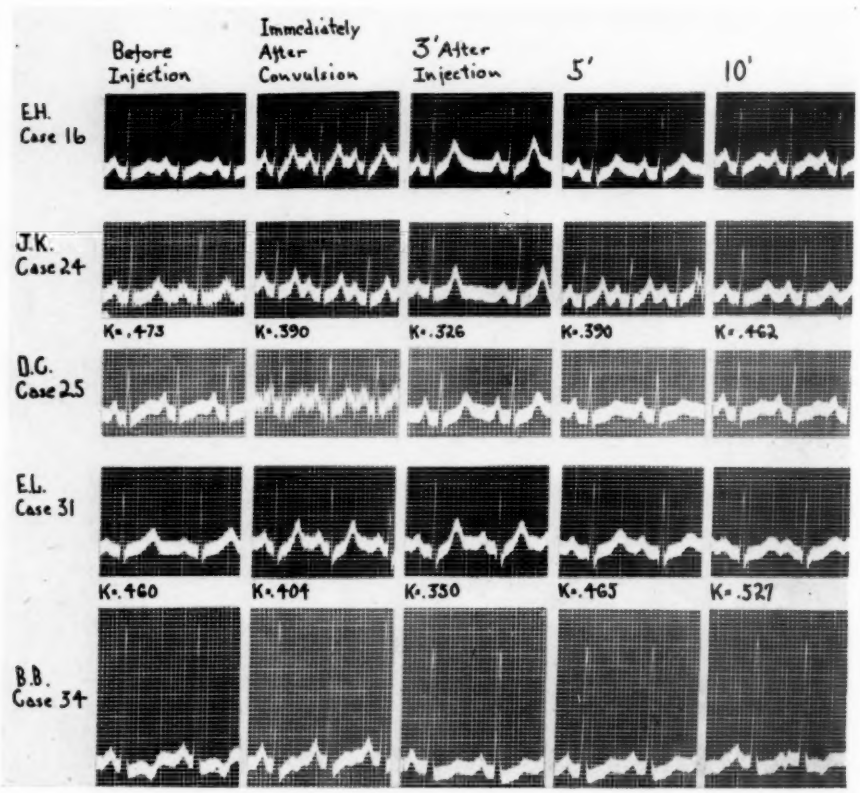

Fig. 4.—Cases in which the principal change following the convulsion was in the magnitude and contour of the T wave. Lead II throughout.

A change in contour accompanied this increase in height of the T wave. This change is illustrated in Fig. 4. The T waves rise more abruptly than in the control curve, are more sharply pointed, and appear narrow, as if the ascending and descending limbs had been pressed closer to-

gether. Barker and his collaborators[10] reported similar changes in the T waves when the blood pH was lowered by the ingestion of ammonium chloride, strenuous exercise, or rebreathing. Low and his co-workers,[11] who studied some of the physiologic changes which accompany metrazol convulsions, found a reduction of the blood pH from a mean fasting level of 7.34 to a mean level of 7.14 ten minutes after the convulsion. Although these authors caution against drawing far-reaching conclusions from such a small number of observations (ten patients, ten controls), it is possible that the changes in the T waves which we observed were the result of a temporary acidosis.

CHANGES IN THE DURATION OF ELECTRICAL SYSTOLE

In order to take into account the variation of electrical systole which occurs with changes in the heart rate, we have applied the formula of Bazett[12] (systole $= K\sqrt{\text{cycle}}$), using K as an expression of the duration of systole. Bazett found that, in normal men, K varied between 0.342 and 0.392, with an average value of 0.368. In normal women, K varied between 0.36 and 0.44, with an average value of 0.399.

In our series it was found that K was reduced (0.030, or more) immediately after the convulsion in thirty-two instances, was increased in eight, and remained unchanged in three. In fourteen cases, K was found to be well above the upper limits of normal ten minutes after the injection of the drug.

In those cases in which K was appreciably reduced, there was a concomitant increase in the amplitude of the T wave; this suggests that these two changes were interdependent. Examples of this association are shown in Fig. 1. The striking variations in K were caused mainly by changes in heart rate without corresponding alterations in the Q-T interval, but in part by changes in the Q-T interval itself.

OBSERVATIONS FOLLOWING SUBCONVULSANT DOSES

Occasionally, during the course of treatment, a dose of metrazol which was ordinarily large enough to produce a convulsion would fail to do so. This was particularly true of the initial treatment. At the outset we had hoped that a study of the changes produced in the electrocardiogram by subconvulsant doses would differentiate the direct effects of the drug alone from the indirect effects of the convulsion. It was soon learned, however, that patients were so disturbed by subconvulsant doses that technically satisfactory records were difficult to obtain. Nine satisfactory records were obtained.

Except for minor deviations, the electrocardiograms which were taken at intervals after such injections in seven patients were not essentially different from those of the controls.

In two cases, however, changes in the cardiac rhythm were conspicuous. Fig. 5 *A* and *B* shows the electrocardiograms in Case 29; one set (5 *A*) was recorded following a subconvulsant dose of metrazol, and

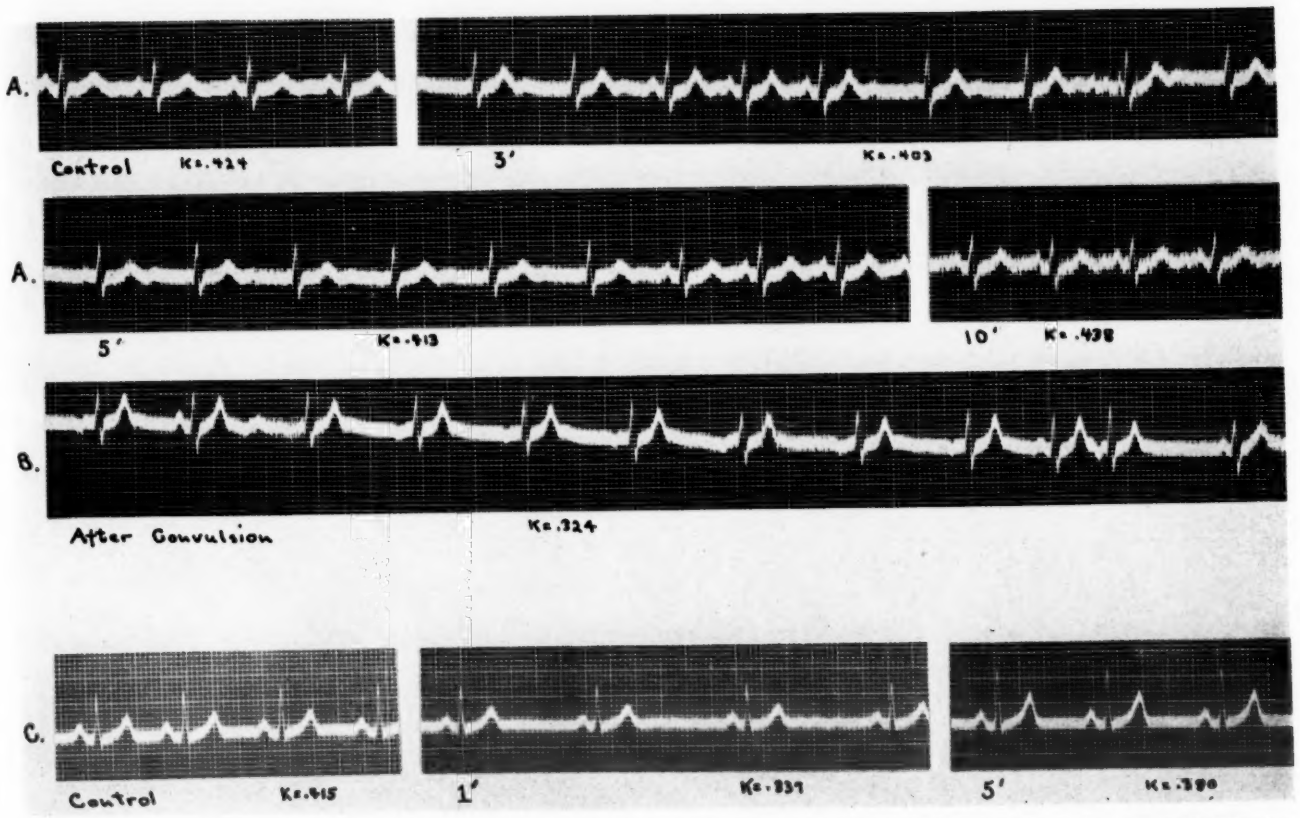

Fig. 5.—Lead II. *A*, Case 29. A-V rhythm 3 and 5 minutes after a subconvulsant dose of metrazol. *B*, Immediately following a convulsion produced by a second injection. In this record there is a change in the contour of the T waves and a reduction in K. *C*, Case 35. Sinus bradycardia following a subconvulsant dose. In this case there are a reduction in K in the three-minute record and an increase in the magnitude of the T waves in the five-minute record.

the other (5 *B*), after a typical convulsion had been produced by a second injection, twenty minutes after the first. In both records atrioventricular and sinus rhythm alternated, although, after the convulsion, the A-V rhythm was more persistent and was accompanied by numerous auricular extrasystoles. The second set of records, but not the first, showed the typical changes in the contour and amplitude of the T wave and in the value of the systolic index "K" which have already been referred to. The value of K was 0.403 during the period of A-V rhythm which was induced by the subconvulsant dose of metrazol, but only 0.324 after the A-V rhythm which followed the convulsion.

The electrocardiograms shown in Fig. 5 *C* were obtained in Case 35, in which there was sinus bradycardia, with a rate of 53 per minute, immediately after a subconvulsant dose. In contrast to the other case illustrated in this figure, the subconvulsant dose of metrazol was followed by an increase in the magnitude of the T waves and a reduction in the value of K from 0.415 to 0.337.

The changes in rhythm which follow the injection of a dose of metrazol which is insufficient to provoke a convulsion may be the result of central vagal stimulation. The modification of the T waves and of K which is sometimes seen under these circumstances cannot be ascribed to the same cause.

CASES IN WHICH THE CARDIOVASCULAR SYSTEM WAS ABNORMAL

Included in this series were five patients whose cardiovascular systems were either questionably normal or definitely abnormal. There was considerable hesitation about recommending metrazol treatment for these patients, but when the hopelessness of their mental state was considered, the risk seemed worth taking. The essential clinical features in these cases are outlined in Table IV. Except for one case of mitral stenosis, the cardiac abnormalities in this group were probably the result of hypertension and arteriosclerosis.

The control electrocardiograms of these five patients are shown in Fig. 6. Contrary to our expectations, the records taken following the convulsion in this group did not differ from those obtained after the convulsion in subjects with normal hearts. The treatments were tolerated equally well and were completed uneventfully in each instance.

In retrospect, however, it seems probable that the successful completion of treatments in these cases was partly the result of good fortune, particularly in Case 34, and to a somewhat less degree in Case 23. In Case 34, in addition to the patient's advanced age of 65 years, there were a consistent elevation of the systolic blood pressure (over 200 mm. Hg) and a grossly abnormal electrocardiogram. Furthermore, the systolic blood pressure rose to 300 mm. Hg immediately after the convulsion on at least two occasions. It could be lowered to its former level by means of amyl nitrite. Judging from this observation, a sustained systolic blood pressure of more than 200 mm. Hg substantially increases the risk of this type of treatment.

TABLE IV

CASES IN WHICH THE CARDIOVASCULAR SYSTEM WAS ABNORMAL

CASE	AGE	PSYCHIATRIC DIAGNOSIS	CARDIAC DIAGNOSIS	HEART SIZE (FLUOROSCOPY AND TELEOROENTGENOGRAM)	BLOOD PRESSURE	ELECTROCARDIOGRAM (SHOWN IN FIG. 6)	NO. OF TREATMENTS
T. E. Case 4 Female	53	Simple depression	Questionably abnormal electrocardiogram	No enlargement	150/90	Left axis deviation not definitely outside normal limits. White's index +24	5
J. C. Case 6 Male	48	Manic depressive, depressed	Hypertensive heart disease; latent syphilis	Enlargement of left ventricle	160/90	Marked left axis deviation. Index +37	12
N. L. Case 23 Female	30	Dementia praecox	Rheumatic heart disease; mitral stenosis and insufficiency	Enlargement of all chambers	150/90	Right axis deviation not definitely outside normal limits. Index −13	31
B. B. Case 34 Female	65	Simple depression	Hypertensive heart disease	Enlargement of left ventricle	215/105	Abnormally large QRS complexes and inverted T waves in Leads I and II	6
T. K. Case 37 Male	50	Simple depression	Hypertensive heart disease	No enlargement	150/110	Rather flat T waves in Lead I, with inversion in Lead II. Left axis deviation. Index +21	7

The only patient in this series with chronic valvular disease (Case 23) tolerated a prolonged course of treatments, thirty-one in all, surprisingly well. It should be emphasized, however, that at no time were there any signs of cardiac failure. Any evidence of cardiac failure would in itself have contraindicated metrazol treatment.

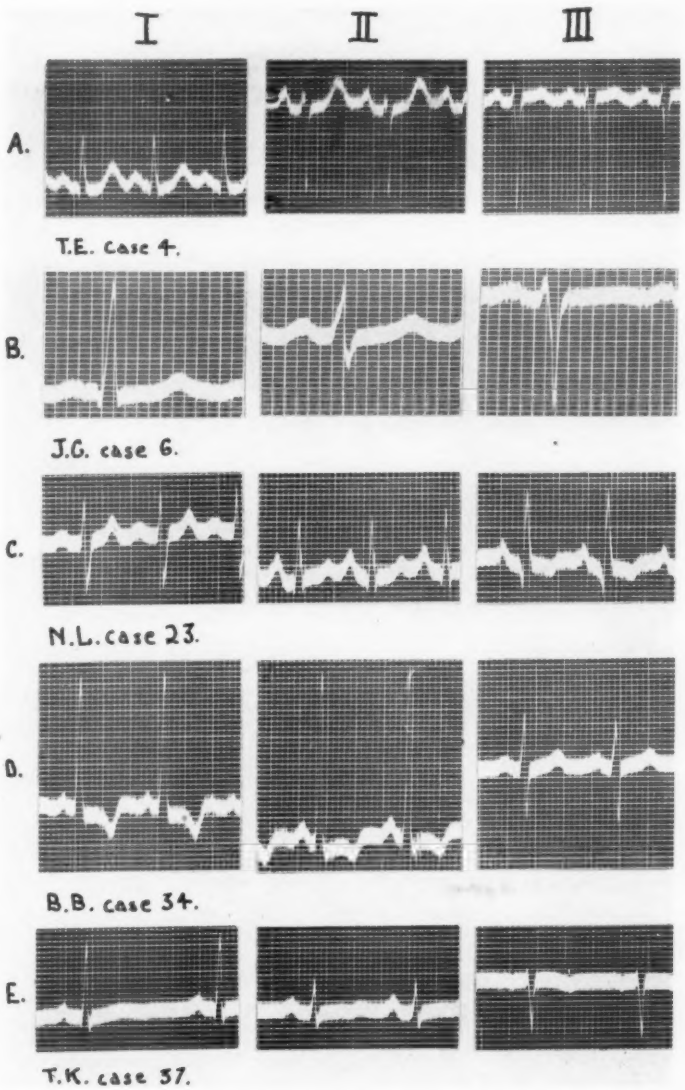

Fig. 6.—Control electrocardiograms of the patients listed in Table IV.

SUMMARY AND CONCLUSIONS

Observations were made following forty-three metrazol-induced convulsions and after nine injections of the drug in amounts which were insufficient to provoke a convulsion. Invariably, there were a rise in

both the systolic and diastolic blood pressure and a change in the heart rate; the latter was inconstant in direction and magnitude.

The most striking disturbances were the frequent and varied arrhythmias which followed most of the convulsant doses and several of those which failed to induce a convulsion. These changes in the cardiac mechanism were probably the result of increased vagal tone and other factors, such as asphyxia.

After the convulsions the T waves of the electrocardiograms became tall and pointed, and the value of the Bazett systolic index (K) was greatly reduced.

No permanent alterations of the cardiac mechanism occurred.

We wish to thank Dr. Harold Feil and Dr. Frank N. Wilson for their help in the preparation of this manuscript.

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THE PERIPHERAL BLOOD FLOW IN HYPERTHYROIDISM

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INTRODUCTION

SINCE 1825, when the posthumous papers of Parry, including a description of hyperthyroidism, were published, clinicians have been impressed by the changes which this disease occasions in the cardiovascular system. Studies have been made of the basal metabolic rate,[1] cardiac output,[2, 3, 4] blood volume and venous pressure,[5, 6] velocity of blood flow,[6, 7] pulse rate and pulse pressure,[8, 9] and vital capacity[10, 11] before and after treatment. The flushed appearance of these patients points to a change in the peripheral circulation. No objective measurements of peripheral circulation, however, have been made.

We have measured, therefore, the peripheral blood flow of eighteen patients who had signs and symptoms of hyperthyroidism (1) when they first came under observation, (2) while they were receiving iodine, and (3) after thyroidectomy. Since the methods we employed were relatively new, a review of pertinent observations is in order.

RÉSUMÉ OF LITERATURE RELATIVE TO RADIATION, CONDUCTION, CONVECTION, AND EVAPORATION

Rubner[12] was the first observer to grasp the significance of heat loss. In 1896, he published a table estimating losses from radiation and convection. The thermal conductance of tissues was first estimated in 1911, by Lefevre.[13] Hill[14] has published excellent studies on the measurement of heat loss, at body temperature, by radiation, convection, and evaporation. More recently, Cobet and Bramigk,[15] and, later still, Bedford and Warner[16] and Bedford[17] have used radiometers in the measurement of skin temperature and the study of heat loss. Bohnenkamp[18, 19] was the first to emphasize the importance of the profile, or effective, radiation surface, which, he found, amounted to approximately 80 per cent of the total body surface. Using an ingeniously constructed jacket of resistance wires, Burton[20, 21] recorded the changes in skin temperature brought about by a measured amount of work. Later, Burton and Murlin,[22] working with a calorimeter and a Burton resistance jacket, gathered data relating to surface area and temperature gradients. Winslow, Herrington, and Gagge[23-26] have made an analysis of all of the physical factors concerning heat loss under a wide variety of environmental conditions; they found large differences between the

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relative proportions of radiation and convection. Their work developed the study of the thermal conductance of the skin. From changes in thermal conductance they calculated the depth of the thermal gradient of the body and measured the peripheral circulation. Using these principles, Hick, Keeton, Glickman, and Wall[27] made studies of normal persons under varying environmental conditions, and calculated an index to peripheral circulation, blood volume, and cardiac output. Burton and Bazett,[28] Bazett,[29] and Bazett and McGlone,[30, 31] have also made fundamental contributions relating to the temperature of the subcutaneous tissues and muscles and the temperature gradients.

CALCULATIONS

A formula has been devised by Hardy and Soderstrom[32] to express the internal thermal exchanges of the body in terms of total blood flow to the skin in cubic centimeters per minute. If the internal (or rectal) temperature, the heat eliminated (that is to say, heat loss), and the average weighted skin temperature are measured, the relative flow of blood to the peripheral tissues may be calculated. Their technique was modified by Stewart and Jack[33] so that average weighted skin temperature, rectal temperature, and basal metabolic rate could be used in the estimation of peripheral blood flow. This modified technique has been followed in our investigations.

With increase in blood flow to the periphery, more heat is brought from the deeper tissues to the surface, so that the thermal conductance of the superficial tissues is increased. Therefore, changes in thermal conductance become an index to peripheral blood flow.

The formula for calculating peripheral blood flow is as follows:[32]

$$\text{I.} \qquad F = 17 \times A \left(\frac{Hl}{MR - MS} - \overset{\circ}{9.1} \; [-\overset{\circ}{6.5}] \right)$$

in which,

F = peripheral conductance above minimal value
17 = factor for converting Cal./C°/M²/Hr. into c.c./min.
A = surface area in sq. meters
Hl = heat loss (for calculation, see Formula II)
MR = mean rectal temperature
MS = mean of average skin temperature
9.1 = kilocals/C°/M²/Hr. (Average thermal conductivity of superficial tissue with minimum blood flow for males in temperatures below 28° C.[32])
6.5 = same as above for females[32]

"F" in this formula measures the heat carried to the surface in excess of heat conducted by the tissues; therefore, it can be taken as a positive index of the volume of blood circulating in the periphery. If blood enters the periphery at rectal temperature and finally reaches the skin at skin temperature, then "F" will measure this flow in cubic centimeters per minute.

In order to use this formula in our observations, it was necessary to compute heat loss (Hl) from the sum of heat produced (Hp) and heat storage (Hs).

II. $Hl = (Hp) + (Hs)$
in which,
Hl = heat loss
Hp = heat produced (calculated from oxygen consumption)
Hs = heat storage (for calculation, see Formula III)
Heat storage is calculated from the following formula:

III. $Hs = W \times 0.8\ [(\triangle R \times 0.8) + (\triangle S \times 0.2)]$
in which,
Hs = heat storage
W = body weight in kilograms
0.8 = average specific heat of body tissues
$\triangle R \times 0.8$ = weighted change in rectal temperature
$\triangle S \times 0.2$ = weighted change in average skin temperature

IV. $\triangle R = R_B - R_E$
in which,
$\triangle R$ = change in rectal temperature
R_B = rectal temperature at beginning of twenty-minute period
R_E = rectal temperature at end of twenty-minute period

V. $\triangle S = S_B - S_E$
in which,
$\triangle S$ = change in average skin temperature
S_B = average skin temperature at beginning of twenty-minute period
S_E = average skin temperature at end of twenty-minute period

Winslow, Herrington, and Gagge[24] have considered heat storage as "positive" or "negative." Using their terminology, positive values for storage correspond to a cooling of the body, and negative values, to a heating of the body. In short, when the temperature falls (see rectal temperatures, pages 721 and 722), "positive storage" occurs, and when the temperature rises (see skin temperatures, pages 721 and 722), "negative storage" occurs. It will be seen later, in the section on example of calculations (pages 721 and 722), that, for the first twenty-minute period "during iodine," in the case of A. S.[I], "negative storage" occurred. Formulas IV and V are based on these principles.

Formula III represents the change in average, weighted, body temperature from one set of rectal and skin temperature readings to the next, multiplied by the body weight and average specific heat of body tissues. From a series of six sets of readings during a morning's observations, we were able to calculate the heat storage (Hs) for five average periods. Substituting the sum of heat produced (Hp) and heat storage (Hs) for heat loss (Hl) into Formula I, the peripheral blood flow was calculated in c.c. per minute for each of the five periods. We have divided this value by the surface area in square meters, in order to express the peripheral blood flow in cubic centimeters per sq. m. per minute (see example of calculation on page 721).

It may be pointed out that Burton,[20, 21] Burton and Murlin,[22] Winslow, Herrington, and Gagge,[23, 24] Du Bois,[34] and Hardy, Du Bois, and Soderstrom[35] have measured heat loss by the method we have employed (Formula II), and compared it with actual measurements of heat loss by direct calorimetry; they obtained results of sufficient accuracy for the purposes of this investigation.

It has been estimated from direct calorimetry[35] that weighting the rectal temperature 80 per cent (0.8 in Formula III), and the skin temperature 20 per cent (0.2 in Formula III), gives an approximation of the average body temperature. Using a different method, Burton[36] arrived at values of 65 and 35 per cent, respectively. All agree that using surface temperatures gives a greater degree of accuracy in calculating the average body temperature, and, although rectal temperature has the larger coefficient, the surface temperature is the more important because it changes more in short periods. Hardy, Du Bois, and Soderstrom[35] have pointed out, that approximately two tenths of the body mass lies within 1 cm. of the skin surface. Winslow, Herrington, and Gagge[37] have found that the average temperature gradient extends 2.2 cm. below the surface. Hardy, Du Bois, and Soderstrom[35] estimated that this gradient was 2.0 cm. Allotment of a weighting of 20 per cent of skin temperature arises from several independent sources. The values for weighting average body temperature and the temperature gradient derived by Hardy, Du Bois, and Soderstrom[35] have been used in our studies.

The improved radiometer devised by Hardy and Soderstrom[38] was employed to record skin temperatures. It is very accurate and rapid, and, by a critical comparison,[39] it now appears to be the best method for securing absolute measurements of skin temperature. Hardy and Muschenheim[40] have demonstrated that, from the standpoint of human radiation, a "perfect black body" is a substance which reflects and transmits none of the far infrared rays, but absorbs them all; or, if heat is traveling in the opposite direction, radiates them all. The validity of measurements of skin temperature by the radiometric method has been upheld by the work of Hardy,[41, 42] Hardy and Muschenheim,[40] and Hardy and Oppel.[43] These investigations show that the human skin is practically a perfect, infrared, "black-body" radiator. Moreover, they have shown that, at the temperature of the human body, the emissions of infrared rays fall between 5μ and 20μ, and that, in this range, there is essentially no difference in the emissivity of the skins of white men and negroes. The "blackness" of the skin is of considerable physiologic importance, for it enables the investigator to calculate skin temperature from radiation.[34] The human skin is slightly more efficient as an insulator than cork;[13, 40, 43] when one lies nude and motionless in the basal state, with the environmental temperature below 28° C., it functions like a dead insulator and is practically bloodless,[42] and the blood flow to the skin, the thermal conductivity of the peripheral tissues, and vaporization are constant.[32, 42] Hardy and Soderstrom[32] have found that the average thermal conductivity of superficial tissues, when blood flow is minimal, is approximately 9.1 kilocals/C°/M²/Hr. for men, and about 6.5 for women (Formula I). These values remain almost constant when the room temperature is below 28° C. However, it is well

known that, for persons with more than the average amount of subcutaneous fat, these values may be too high.

METHODS

In order to measure the peripheral blood flow according to the method devised by Hardy and Soderstrom[32] (Formula I), it was necessary to secure certain data, namely, recordings of skin and of rectal temperatures, of oxygen consumption, of height, and of body weight. In addition, observations were made on blood pressure, arm-to-tongue circulation time, and pulse rate.

The room in which our studies were carried out was small and compact; it had one small door, one window, and a steam radiator. The humidity was not measured; since most of the observations were made during the winter months, and because of the steam radiator, it must necessarily have been low. Heat loss from convection was kept at a minimum by placing a metal screen in front of the window. Patients lying flat in bed perspire in those parts which are in contact with the mattress. It was impossible to prevent this. (In the Russell Sage calorimeter, in which subjects lie on a bed made of heavy fishing line, this factor, as well as conduction, is eliminated.) Under our environmental conditions, however, conduction and vaporization were reduced to a minimum, for the room temperature was kept within the cool zone of approximately 23° to 27° C. Close attention to the door, window, and radiator enabled us to keep the temperature of the room constant within ± 0.5° C. during all observations on any patient. The observations on one of the earlier patients were discarded because the room temperature during the three periods of investigation showed too great variation.

Skin temperatures were measured at eleven points of uniform area on the anterior surface of the body (Fig. 1), using a Hardy-Soderstrom radiometer[38] which was calibrated to read directly in degrees centigrade on a galvanometer scale. These skin temperatures were weighted according to the surface of the body which they represented (Hardy, et al.,[35] p. 466) (Fig. 1).

Rectal temperatures were measured by means of a single-junction thermocouple,[38] one end of which was immersed in a pint thermos flask filled with warm water kept at body temperature; the other end, which was silver-tipped, was inserted into the rectum for approximately 10 cm. as soon as the patient came to the room, and remained in place throughout the morning. The connections were arranged so that readings could be made from the galvanometer scale of the radiometer, which was calibrated to show degrees centigrade directly. The readings are accurate to ± 0.02° C.[38, 39]

Oxygen consumption was measured with a Benedict-Roth metabolism apparatus.[44] The basal metabolic rate was calculated from the Mayo Foundation Standards for age and sex,[45] and the surface area was estimated from the tables of Du Bois and Du Bois.[46]

Blood pressures were measured with a standard mercury sphygmomanometer, and in accordance with the joint recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland.[47]

The arm-to-tongue circulation time was measured by means of decholin;[7] 5 c.c. of a 20 per cent solution were injected rapidly (one to two seconds) through an 18-gauge needle into an antecubital vein while the subject was lying quietly in the supine position. This was repeated in one and one-half minutes. The time was recorded from the beginning of the injection until the subject first perceived the bitter taste.

PROCEDURE

The procedure was similar for all patients. Most of them were in the hospital several days before the first studies were made. During this time they became

accustomed to hospital routine, but were not trained for the procedures. Since one of the characteristics of Graves' disease is emotional instability, all of the patients were assured that the procedures would have no harmful effect. The use of the radiometer and our plan of investigation were outlined to each. During the various phases of our study all of the subjects cooperated well.

All of the observations were made in the morning, when the patients were in a basal metabolic state. The patients, lying nude in bed with the rectal thermometer in place, were covered only by a sheet. During the first hour, when the subjects were adjusting to the environment, no observations were made.

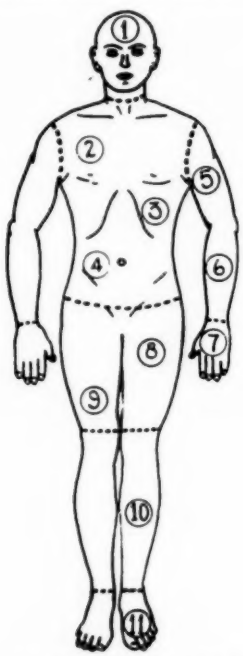

Fig. 1.—This figure shows the locations of eleven areas over the anterior surface of the body where skin temperatures were measured with the Hardy-Soderstrom radiometer. Weightings for the divisions of body surface, totaling 1.00, are: Head, *1*, = 0.07; trunk, *2*, *3*, *4*, = 0.35; arms, *5*, *6*, = 0.14; hands, 7, = 0.05; thighs, *8*, *9*, = 0.19; legs, *10*, = 0.13; and feet, *11*, = 0.07. (Hardy and Du Bois,[35] p. 466.) The sum of the weighted temperature of each area equals the average skin temperature:

$$[(T_1 \times 0.07) + (\frac{T_2 + T_3 + T_4}{3} \times 0.35) + (\frac{T_5 + T_6}{2} \times 0.14) + (T_7 \times 0.05) + (\frac{T_8 + T_9}{2} \times 0.19) + (T_{10} \times 0.13) + (T_{11} \times 0.07)] = S.$$

The order in which data were collected was as follows: First, the oxygen consumption was measured. The room temperature was then noted, after which the temperatures of the skin of the eleven areas (Fig. 1) were recorded. The rectal temperature was then measured. The same procedure was repeated, at intervals of twenty minutes, until a series of six separate readings had been obtained; from these the peripheral blood flow was calculated for five average periods. The blood pressure was measured and the pulse rate counted during free intervals. After completing the recordings of skin and rectal temperatures, the oxygen consumption was measured again, followed by estimations of the arm-to-tongue circulation time. Subsequent studies were made in exactly the same sequence "during iodine" and "after operation," and the environmental conditions were duplicated as nearly as possible. Throughout this paper the terms "before iodine," "during iodine," and "after operation" are used to indicate that these patients were first studied before the institution of iodine therapy, while receiving iodine,

usually one to two days before operation, and in the latter part of their convalescence from subtotal thyroidectomy, respectively.

EXAMPLE OF THE CALCULATION OF PERIPHERAL BLOOD FLOW

The following data were obtained in the case of patient A. S.[1] during the first two periods of observation "during iodine" (Fig. 2). By using these data in the appropriate formulas (pages 716 and 717), peripheral blood flow for the first twenty-minute period is calculated as follows:

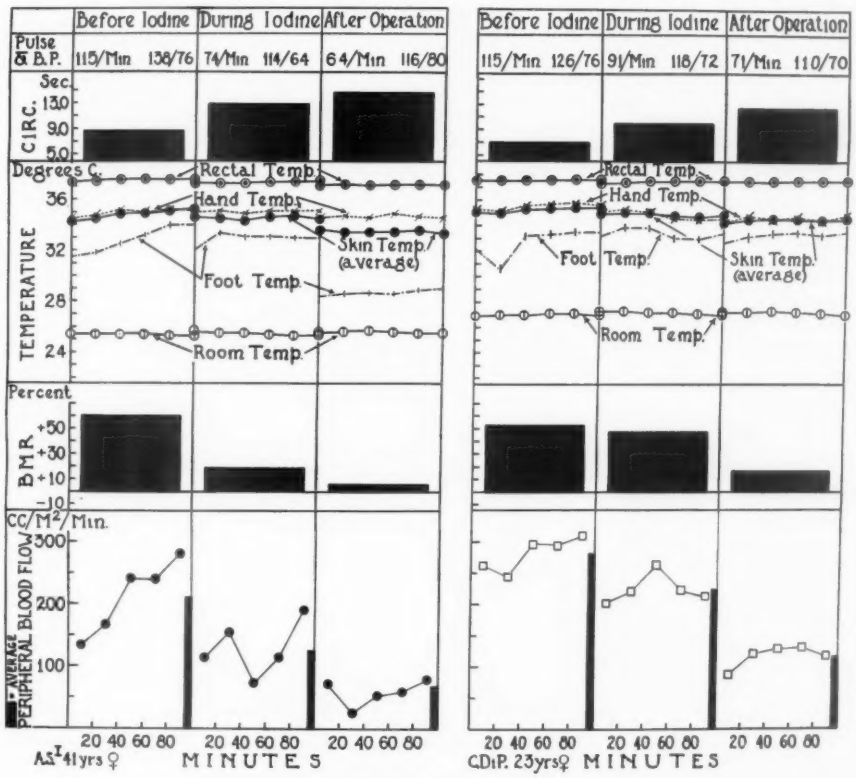

Fig. 2.—In this figure there are plotted data relating to patients A. S.[1] and C. DiP. to show the effect of room temperature on peripheral blood flow. Average peripheral blood flow is indicated by the solid column at the end of each phase. "Before iodine," the peripheral blood flow was less in patient A. S.[1] than in patient C. DiP. at the higher room temperature. There was only a rough correlation between the temperature of the hands and feet and average skin temperature; this was particularly the case with respect to the feet.

The average skin temperature (p. 722, column 4) was derived by weighting the skin temperatures of the eleven areas shown in Fig. 1 (Hardy, et al.,[35] p. 466). For example, the average skin temperature at the beginning of the first twenty-minute period was calculated in the following manner:

$$S_B = [(T_1 \times 0.07) + (\frac{T_2 + T_3 + T_4}{3} \times 0.35) + (\frac{T_5 + T_6}{2} \times 0.14) + (T_7 \times 0.05) + (\frac{T_8 + T_9}{2} \times 0.19) + (T_{10} \times 0.13) + (T_{11} \times 0.07)] = [(35.4 \times 0.07) + (\frac{35.0 + 35.7 + 34.9}{3} \times 0.35) + (\frac{33.2 + 34.1}{2} \times 0.14) + (35.0 \times 0.05) + (\frac{33.7 + 32.7}{2} \times 0.19) + (33.2 \times 0.13) + (32.0 \times 0.07)] = 34.13° \text{ C.}$$ (See p. 722.)

The average skin temperature at end of twenty-minute period S_E was calculated in a similar manner.

Name: A. S.[1]
Age: 41 years
Height: 166.0 cm.
Weight: 71.1 kg.

Sex: Female
B.M.R. +18 per cent

Total heat production, from oxygen consumption, 75.7 cal./hr.
Total surface area, 1.80 sq.m. = A

Time (A.M.)	Room Temperature (°C.)	Rectal Temperature (°C.) = R (p. 723)	Average Skin Temperature (°C.) = S (p. 721)	Skin Temperature (Radiometer) from Areas Shown in Fig. 1 = T										
				T_1 (°C.)	T_2 (°C.)	T_3 (°C.)	T_4 (°C.)	T_5 (°C.)	T_6 (°C.)	T_7 (°C.)	T_8 (°C.)	T_9 (°C.)	T_{10} (°C.)	T_{11} (°C.)
10:10	25.6	$37.28 = R_B$	$34.13 = S_B$	35.4	35.0	35.7	34.9	33.2	34.1	35.0	33.7	32.7	33.2	32.0
10:30	25.5	$37.23 = R_E$	$34.49 = S_E$	35.2	35.2	35.7	35.2	33.6	34.2	35.2	34.5	33.5	33.1	33.7

The rectal temperatures at the beginning (R_B) and the end (R_E) of the first twenty-minute period were 37.28° C. and 37.23° C., respectively. The average skin temperatures at the beginning (S_B) and the end (S_E) were 34.13° C. and 34.49° C., respectively.

Substituting in Formula IV,

$$\begin{aligned}\triangle R &= R_B - R_E \\ &= 37.28^\circ \text{ C.} - 37.23^\circ \text{ C.} \\ &= +0.05^\circ \text{ C.}\end{aligned}$$

Likewise, substituting in Formula V,

$$\begin{aligned}\triangle S &= S_B - S_E \\ &= 34.13^\circ \text{ C.} - 34.49^\circ \text{ C.} \\ &= -0.36^\circ \text{ C.}\end{aligned}$$

Substitute the values derived by Formulas IV and V into Formula III for the calculation of heat storage (Hs).

$$\begin{aligned}Hs &= W \times 0.8\,[(\triangle R \times 0.8) + (\triangle S \times 0.2)] \\ Hs &= 71.1 \times 0.8\,[(+0.05 \times 0.8) + (-0.36 \times 0.2)] \\ &= 56.9\,[(+0.040) + (-0.072)] \\ &= 56.9\ (-0.032) \\ &= -1.82 \text{ cal./20 min.}\end{aligned}$$

Since −1.82 cal. is the heat storage for a twenty-minute period, to derive the heat storage for one hour, multiply by 3:

$$\begin{aligned}Hs &= 3 \times (-1.82 \text{ cal.}) \\ &= -5.46 \text{ cal./hr.}\end{aligned}$$

Referring to Formula II,

$$\begin{aligned}Hl &= (Hp) + (Hs) \\ &= (75.70 \text{ cal./hr.}) + (-5.46 \text{ cal./hr.}) \\ &= 70.24 \text{ cal./hr.}\end{aligned}$$

To reduce to cal./sq.m./hr., divide by surface area (1.80 sq.m.):

$$\begin{aligned}Hl &= \frac{70.24 \quad \text{cal./hr.}}{1.80 \quad \text{sq.m.}} \\ &= 39.0 \text{ cal./sq.m./hr.}\end{aligned}$$

Calculations of the mean rectal and the mean of the average skin temperatures (MR and MS, respectively, in Formula I) for the first twenty-minute period were as follows:

VI. $$\begin{aligned}MR &= \frac{R_B + R_E}{2} \\ &= \frac{37.28^\circ \text{ C.} + 37.23^\circ \text{ C.}}{2} \\ &= 37.26^\circ \text{ C.}\end{aligned}$$

and,

VII. $$\begin{aligned}MS &= \frac{S_B + S_E}{2} \\ &= \frac{34.13^\circ \text{ C.} + 34.49^\circ \text{ C.}}{2} \\ &= 34.31^\circ \text{ C.}\end{aligned}$$

As a final step, substitute the values for heat loss (Hl), the mean rectal temperature (MR), and the mean of the average skin temperature (MS) into Formula I, using −6.5 as the average thermal conductivity for females:

$$\begin{aligned}F &= 17 \times A\ \left(\frac{Hl}{MR - MS} - 6.5\ ♀\right) \\ &= 17 \times 1.80\ \left(\frac{39.0}{37.26 - 34.31} - 6.5\right) \\ &= 30.6\ \left(\frac{39.0}{2.95} - 6.5\right) \\ &= 30.6\ (13.2 - 6.5) \\ &= 30.6 \times 6.7 \\ &= 205 \text{ c.c./min.}\end{aligned}$$

Reducing the blood flow to c.c./sq.m./min., since the surface area was known,

$$F = \frac{205 \text{ c.c./min.}}{1.80 \text{ sq.m.}}$$

$$= 114 \text{ c.c./sq.m./min.},$$

which was the average peripheral blood flow for the first twenty-minute period "during iodine" (Fig. 2).

Peripheral blood flow, as we have calculated it, is an expression of the average of total peripheral response to changes in the vascular tree, and is a measure of the total amount of blood allocated to the periphery of the whole body, or to each square meter of body surface when this is divided by the surface area. The result is expressed in cubic centimeters per square meter per minute. We are of the opinion that a much more accurate index of peripheral circulation is obtained by this means than by estimations of circulation in an isolated extremity or digit by recording its skin temperature or its changes in volume. The temperature of the hands and feet is deceptive, as was pointed out by Du Bois.[34] Our observations confirm this; therefore, the conception of peripheral blood flow as an average total surface function appears to be the proper approach to this problem.

OBSERVATIONS

Peripheral Blood Flow and Basal Metabolic Rate.—"Before iodine," the highest, lowest, and *average* basal metabolic rates were +83, +21, and *+45* per cent, respectively; and the highest, lowest, and *average* peripheral blood flows were 235, 134, and *182* c.c. per square meter per minute, respectively (Figs. 3 and 4) (Table I). In short, in the "before iodine" phase, when the basal metabolic rate was high, the peripheral blood flow was also elevated.

TABLE I

AVERAGE VALUES OF DATA RELATING TO EIGHTEEN PATIENTS WITH HYPERTHYROIDISM

	BEFORE IODINE	DURING IODINE	AFTER OPERATION
Basal metabolic rate	45%	23%	9%
Peripheral blood flow	182 c.c./M²/min.	109 c.c./M²/min.	55 c.c./M²/min.
Skin temperature	34.58° C.	33.58° C.	33.08° C.
Temperature of hands	34.7° C.	34.0° C.	34.0° C.
Temperature of feet	32.4° C.	31.0° C.	29.7° C.
Rectal temperature	37.32° C.	37.24° C.	37.28° C.
Circulation time	9.1 sec.	10.2 sec.	12.6 sec.
Pulse rate	104/min.	86/min.	81/min.
Pulse pressure	58 mm. Hg	47 mm. Hg	43 mm. Hg
Peripheral resistance	.74 mm. Hg/c.c./M²/min.	1.34 mm. Hg/c.c./M²/min.	3.12 mm. Hg/c.c./M²/min.

"During iodine," the highest, lowest, and *average* basal metabolic rates were +48, +5, and *+23* per cent, respectively; and the highest, lowest, and *average* peripheral blood flows were 225, 50 and *109* c.c. per square meter per minute, respectively. All patients "during iodine" showed a fall in basal metabolic rate and peripheral blood flow.

"After operation," the highest, lowest, and *average* basal metabolic rates were +19, +3, and *+9* per cent, respectively; and the highest, lowest,

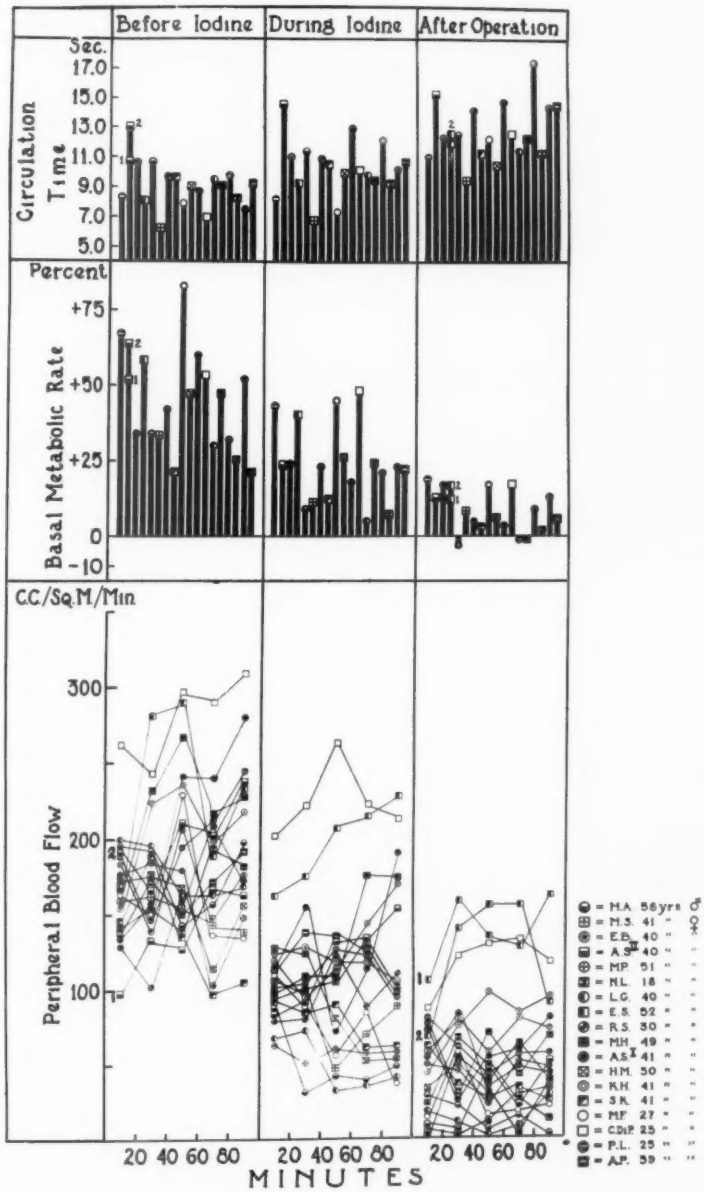

Fig. 3.—In this figure there are plotted for all patients the peripheral blood flow, basal metabolic rate, and circulation time "before iodine," "during iodine," and "after operation." Each patient is indicated by a symbol. In the case of A. S.[II], who had auricular fibrillation "before iodine," studies were made before, and again after, digitalization (indicated by *1* and *2*, respectively). Because patient E. S. was subjected to a two-stage subtotal thyroidectomy, observations were made on two occasions "after operation" (indicated by *1* and *2*, respectively).

and *average* peripheral blood flows were 137, 9, and *55* c.c. per square meter per minute, respectively. Finally, further decreases in basal metabolic rate and peripheral blood flow were observed "after operation." It may be recalled that Hardy and Soderstrom[32] found in normal subjects that the average peripheral blood flow was 15 c.c. per square meter per minute at temperatures below 28° C.

Average Skin Temperature.—"Before iodine," the highest, lowest, and *average* skin temperatures were 35.24° C., 32.97° C., and *34.58°* C., respectively (Table I). "During iodine," the highest, lowest, and *average* skin temperatures were 34.90° C., 31.67° C., and *33.58°* C., respectively. "After operation," the highest, lowest, and *average* skin temperatures were 34.52° C., 30.53° C., and *33.08°* C., respectively. The skin temperature, therefore, continued to decrease through the period of iodine therapy and after operation.

Temperature of the Hands and Feet.—"Before iodine," the highest, lowest, and *average* temperatures of the hands were 35.5° C., 31.4° C., and *34.7°* C., respectively (Table I). "During iodine," the highest, lowest, and *average* temperatures of the hands were 35.4° C., 32.2° C., and *34.0°* C., respectively. "After operation," the highest, lowest, and *average* temperatures of the hands were 35.3° C., 32.7° C., and *34.0°* C., respectively.

"Before iodine," the highest, lowest, and *average* temperatures of the feet were 34.6° C., 22.1° C., and *32.4°* C., respectively (Table I). "During iodine," the highest, lowest, and *average* temperatures of the feet were 33.8° C., 24.6° C., and *31.0°* C., respectively. "After operation," the highest, lowest, and *average* temperatures of the feet were 33.3° C., 25.0° C., and *29.7°* C., respectively.

Rectal Temperature.—The rectal temperature showed no significant changes. The greatest range of change in any one subject during the various periods of observations was ±0.25° C., as, for example, in patient A. S.[I] (Fig. 2). A single exception will be discussed later (page 731, A. S.[II]). The average rectal temperature for the group "before iodine" was 37.32° C., "during iodine," 37.24° C., and "after operation," 37.28° C. (Table I).

The temperatures of the hands were, in most instances, in a zone between average skin temperature and rectal temperature, whereas the temperatures of the feet usually fluctuated between average skin temperature and room temperature.

Circulation Time.—"Before iodine," the circulation time was short; the *average* was *9.1* sec. for the group (Fig. 4) (Table I). The shortest during this period was 6.0 sec., and the longest, 13 sec. (Fig. 3). "During iodine," the *average* circulation time for all patients was *10.2* sec., the shortest, 6.8 sec., and the longest, 14.5 sec. "After operation," the *average* circulation time for the group was *12.6* sec., the shortest, 9.4 sec., and the longest, 17.4 sec. In short, a definite but not striking

increase in circulation time occurred during treatment with iodine, and the time approached normal after operation.

Pulse Rate.—The *average* pulse rate was *104* per minute "before iodine"; the highest was 115 per minute, and the lowest, 87 per minute (Table I). "During iodine," the *average* pulse rate was *86* per minute, the highest, 119 per minute, and the lowest, 70 per minute. "After operation," the *average* pulse rate was *81* per minute, the highest, 100 per minute, and the lowest, 64 per minute. The pulse rates in all cases showed decreases which ran parallel with the fall in basal metabolic rate and peripheral blood flow.

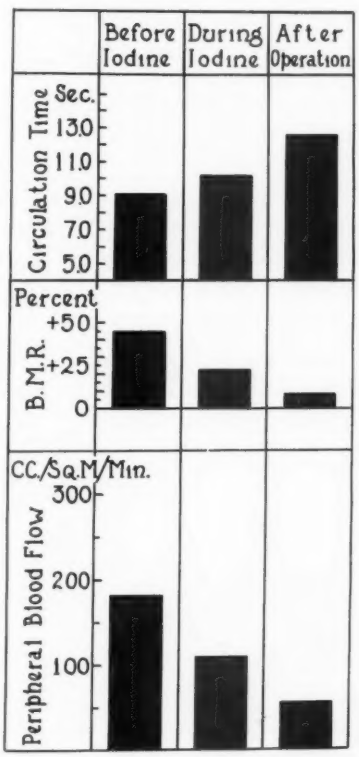

Fig. 4.—In this figure there are plotted the average peripheral blood flow, average basal metabolic rate, and average circulation time for the eighteen patients.

Pulse Pressure.—The pulse pressure was relatively large "before iodine" in all but two cases. The *average* was *58* mm. Hg (Table I). It fell to *47* mm. Hg "during iodine," and to *43* mm. Hg "after operation." The highest recorded "before iodine" was 81 mm. Hg, and the lowest, 35 mm. Hg. The highest "during iodine" was 68 mm. Hg, and the lowest, 30 mm. Hg. "After operation," the highest was 75 mm. Hg, and the lowest, 26 mm. Hg.

Peripheral Resistance.—Since the flushed appearance of these patients suggests peripheral vasodilatation, an estimation of peripheral resis-

tance during the various stages was made. The average systolic blood pressure, in millimeters of mercury, for each experimental period of observation was divided by the average blood flow in cubic centimeters per square meter per minute. The result was expressed as the pressure, in mm. Hg, which was required to force 1 c.c. of blood through 1 sq. m. of skin surface per minute. The *average* pressure required "before iodine" was 0.74 mm. Hg; "during iodine" it rose to 1.34 mm. Hg, and "after operation" to 3.12 mm. Hg per cubic centimeter per square meter per minute (Table I).

DISCUSSION

In every case, the peripheral blood flow was large at first, at a time when the basal metabolic rate was increased. The flow diminished after giving iodine, when the basal metabolic rate had decreased, and this was followed by a still further decrease in flow and fall in basal metabolic rate after subtotal thyroidectomy. Moreover, when the data for all patients were pooled and blood flow was plotted against basal metabolic rate, a linear relationship was revealed (Fig. 5); high basal metabolic rates were associated with an increase in peripheral blood flow, and a progressive decrease in peripheral blood flow occurred with the decrease in basal metabolic rate.

In the period "before iodine," and again "during iodine," the wide fluctuations in peripheral blood flow (Fig. 3) were interpreted as evidence of vasomotor instability. Clinically, it was apparent during the course of a morning's observations that the flushing of the skin became deeper at times, as if the peripheral vascular tree were undergoing intermittent periods of increased vasodilatation. "After operation," fluctuations in peripheral blood flow were less marked (Fig. 3).

The scattering of peripheral blood flow at various levels among individual patients during the three stages of study (Fig. 3) was caused partly by differences in basal metabolic rate, and partly by differences in room temperature. Hick, Keeton, Glickman, and Wall[27] showed that blood flow to the periphery increased as the environmental temperature increased. Certain of our data point to the same conclusion. To illustrate this point, we have plotted the data for two patients so that they may be compared (Fig. 2). The room temperature during observations on patient A. S.[1] remained near 25.5° C., whereas, in the case of patient C. DiP., it was approximately 1.5° C. higher. Although the basal metabolic rate, pulse rate, and pulse pressure were approximately the same "before iodine," the average blood flow was 69 c.c. per square meter per minute greater in the case of C. DiP. at the higher room temperature. The average skin temperature usually showed a similar response to room temperature. This was only roughly true, however, of the temperature of the hands and feet. It was because of the important role played by environmental temperature on blood flow that care was exercised to carry out all observations on any one patient at approximately the same room temperature.

The skin of these thyrotoxic patients appeared hot and flushed when they were first seen, even under basal conditions. This indicated an increase in average skin temperature and peripheral blood flow. Our objective data confirm this clinical impression. "Before iodine," the average skin temperature and peripheral blood flow were elevated at a time when the basal metabolic rate was high, and with the decrease in basal metabolic rate "during iodine," and again "after operation," there was a progressive and parallel decrease in average skin temperature and peripheral blood flow.

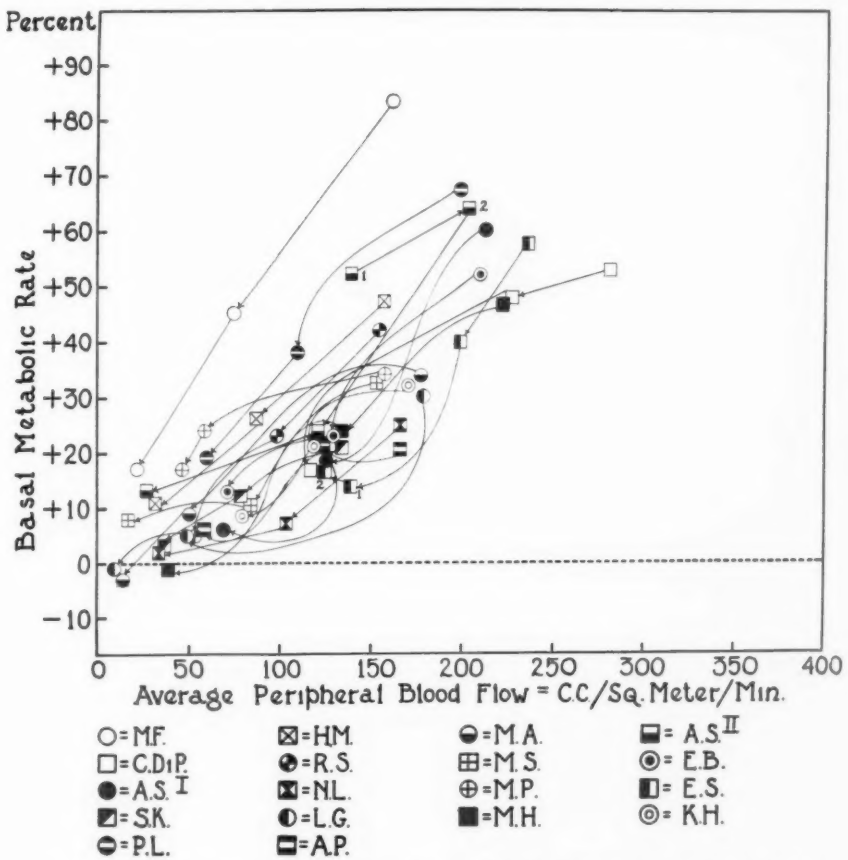

Fig. 5.—In this figure the data for peripheral blood flow in cubic centimeters per square meter per minute are plotted against corresponding basal metabolic rates. The symbols for each patient are connected by arrows to aid in following each patient through the various phases. There is a linear relationship, for, with a decrease in basal metabolic rate, the peripheral blood flow also decreased.

There was no correlation between the temperature of the hands and feet and average skin temperature (Fig. 2). The average temperature of the hands was higher in all instances than average skin temperature. Between the first and second periods of observation, average skin temperature fell 1.0° C., while the temperature of the hands decreased 0.68°

C. Comparison of the periods "during iodine" and "after operation" showed that average skin temperature decreased 0.50° C., but that of the hands decreased only 0.05° C. For the most part, however, the temperature of the hands followed more closely the changes in average skin temperature than did the temperature of the feet (Fig. 2). The temperature of the feet was approximately 2.0° C. to 4.0° C. below average skin temperature, underwent more rapid and wider fluctuations than that of the hands (Fig. 2), and was, at times, below room temperature when this was approximately 23.0° C. It is known that the temperature of the hands and feet is extremely labile. Moreover, the palmar and plantar surfaces perspire freely. The temperatures of the dorsal surface of the hand and the extensor surface of the foot were recorded, therefore, in order to eliminate, as far as possible, the effects of perspiration on skin temperature. Mittelmann and Wolff[48] have shown that the hands respond rapidly and widely to emotion. Du Bois[34] found that the feet cooled too rapidly. Because of these factors, it appears to us that the estimation of peripheral blood flow by measuring skin temperatures or volume changes of an extremity or digit would often be not only a very rough index of peripheral blood flow, but frequently a misleading index. We emphasize again that we measure average peripheral blood flow for the whole surface area. Although there may be general vasodilatation, there may be, at the same time, very marked local vasoconstriction; this occurs, as Hardy* has shown, after giving adrenalin.

The rectal temperature showed a remarkable constancy. "During iodine" the average temperature was 0.08° C. lower than "before iodine." "After operation" there was a rise of 0.04° C. The change, therefore, from the time the patients were first seen until after subtotal thyroidectomy was only 0.04° C. It may be recalled that the average change in skin temperature between the first and second periods was 1.00° C., and that a further decrease of 0.50° C. occurred between the second and third periods, making a total decrease of 1.5° C. This emphasizes a point which was made earlier, namely, that, although the rectal temperature has the larger weighting (80 per cent), the changes in weighted skin temperature (20 per cent) are more important in the estimation of peripheral blood flow.

Two of the patients require discussion because four sets of observations were made, instead of three.

Patient E. S. (History No. 100740), because of her age and of marked thyrotoxicosis, was subjected to a two-stage operation. "Before iodine," the basal metabolic rate was +58 per cent, and the average peripheral blood flow, 235 c.c. per square meter per minute. A decrease of basal metabolic rate to + 40 per cent, and of peripheral blood flow to 198 c.c. per square meter per minute, took place "during iodine." Following removal of the right lobe of the thyroid on Feb. 27,

*Personal communication.

1940, the basal metabolic rate fell to +14 per cent and the peripheral blood flow to 137 c.c. per square meter per minute. Removal of the left lobe was performed March 11, 1940. Although the basal metabolic rate remained essentially the same (+17 per cent), further decrease in peripheral blood flow, to 123 c.c. per square meter per minute, occurred (Fig. 3). Moreover, this patient had the highest pulse rate of the group, not only "before iodine" (115 per minute), but also "after operation." On the first day after removal of the right lobe, the cardiac mechanism changed to auricular fibrillation. With the administration of digitalis, normal sinus rhythm recurred within thirty-six hours, and persisted. On the day of our observations, when the patient was under the influence of digitalis, her pulse rate was 99 per minute. With continuance of digitalis, during observations after removal of the left lobe, the pulse rate was 100 per minute. Average skin temperature, pulse pressure, peripheral resistance, and velocity and blood flow during the four periods showed changes, however, which were similar to those exhibited by the whole group.

In the case of patient A. S.[II] (History No. 260735), an extra set of observations was made "before iodine" because of the presence of auricular fibrillation. No signs of congestive heart failure were present. The basal metabolic rate, average peripheral blood flow, and circulation time were +52 per cent, 138 c.c. per square meter per minute, and 10.8 sec., respectively (Fig. 3). She was given digitalis, and the basal metabolic rate increased to +64 per cent; the average peripheral blood flow now measured 203 c.c. per square meter per minute, that is to say, it increased, and the circulation time was 13.0 sec. Maintenance doses of digitalis were continued, with the addition of iodine therapy. The basal metabolic rate fell to +24 per cent, the peripheral blood flow to 120 c.c. per square meter per minute, and the circulation time increased further to 14.5 sec. After subtotal thyroidectomy, the basal metabolic rate fell to +13 per cent, the peripheral blood flow to 26 c.c. per square meter per minute, and the circulation time increased still further, to 15.2 sec. The average rectal temperatures during the four periods of observation were 37.30° C., 37.81° C., 37.17° C., and 37.30° C., respectively. In short, there was a rise of 0.51° C. after digitalization, but before the institution of iodine therapy. The reason for the rise in rectal temperature in this patient requires consideration. Steele[49] concluded from a series of observations that elevation of rectal temperature may be brought about by obstruction to the peripheral circulation. In other studies he found that there was a rise in rectal temperature in patients with auricular fibrillation and heart failure.[50] The possibility of infection was eliminated in his cases. He attributed the elevation of rectal temperature to a deficiency in ability to lose heat, caused by slowing of the circulation. In our patient, the rise in rectal temperature was not brought about by peripheral circulatory obstruction, for the peripheral blood flow and average skin temperature

were increased at this time as a result of hyperthyroidism. With the disappearance of signs of heart failure, under digitalis therapy, the rectal temperature fell to normal in Steele's cases. Our subject showed no signs of heart failure, and, on digitalization, there was a sharp rise, not a fall, in rectal temperature. Between the first and second series of observations there was a rise of 12 per cent in basal metabolic rate and an increase in circulation time of 2.2 seconds. It has been shown by Stewart, Crane, Deitrick, and Thompson[51] that digitalis increases the work accomplished by the heart per beat, in relation to the cardiac size, whether the rhythm is normal or auricular fibrillation is present. We are of the opinion that the increase of 0.51° C. in average rectal temperature was caused by an excess of heat production over heat loss, in the amount of approximately 1 cal./hr. This was more than adequate to raise the rectal temperature 0.51° C. The increase in peripheral blood flow and average skin temperature after digitalization appears to have been caused by improvement in the general circulation in a patient whose tissue metabolism was increased as a consequence of hyperthyroidism.

The cardiac output is increased in thyrotoxicosis[2, 3, 4] and decreases with the administration of iodine, and again after subtotal thyroidectomy. We measured the cardiac output of one patient, A. S.[1] (History No. 230995), in order to correlate it with the peripheral blood flow. Because each of these procedures requires most of a morning, it was not possible to carry out both on the same day and still keep the patient under basal conditions. The volume output of the heart was therefore measured on the day following studies of peripheral blood flow. The patient was trained for this procedure beforehand. The cardiac output was estimated by the acetylene method; three samples of gas were taken, as recommended by Grollman,[52] and Grollman, Friedman, Clark, and Harrison.[53] The procedure was exactly the same as that which we followed on another occasion.[54] "Before iodine," at a time when the basal metabolic rate was +60 per cent and the peripheral blood flow 212 c.c. per square meter per minute, the cardiac output measured 3.48 liters per square meter per minute (arteriovenous oxygen difference, 54.6 c.c., oxygen consumption, 336 c.c. per minute, stroke volume, 61.5 c.c. per beat). "During iodine," at a time when the basal metabolic rate and peripheral blood flow were +18 per cent and 125 c.c. per square meter per minute, respectively, the cardiac output was 2.53 liters per square meter per minute (arteriovenous oxygen difference, 55.6 c.c., oxygen consumption, 251 c.c. per minute, stroke volume, 60 c.c. per beat). "After operation," when the basal metabolic rate was +6 per cent and the peripheral blood flow 69 c.c. per square meter per minute, the cardiac output was 2.02 liters per square meter per minute (arteriovenous oxygen difference, 57.7 c.c., oxygen consumption, 207 c.c. per minute, stroke volume, 53 c.c. per beat); these values were within the normal range. These data show that there was

an increased output of blood from the heart during the hyperthyroid stage which was adequate to supply the increased amount of blood allocated to the peripheral circulation.

The circulation time was recorded in order to correlate another factor, in addition to basal metabolic rate, with peripheral blood flow. When the basal metabolic rate and peripheral blood flow were elevated, the velocity of blood flow was increased. When these decreased during iodine therapy, and again after subtotal thyroidectomy, the velocity of blood flow also decreased in a parallel fashion (Fig. 4) (Table I).

There is a marked increase in oxygen requirements in hyperthyroidism. The organism attempts to provide this by increasing the volume output of blood.[2-4] Another compensatory measure may be the increase in circulating blood volume.[5, 6] The partition of the cardiac output to the various parts of the body in man is not known, although Levy and Blalock[55] have made some approximations in dogs. In hyperthyroidism, however, there is an ample increase in the total volume output of blood from the heart to provide for the increased amount of blood supplied to the periphery. Nevertheless, the heart is able to keep the blood moving at an increased velocity. We have shown that the peripheral resistance during this time is low. Boothby and Rynearson[4] have observed that in hyperthyroidism there is a greater increase in circulation rate than occurs in a normal subject as a result of a corresponding increase in oxygen consumption caused by work. They suggested that there might be a special circulatory stimulant in hyperthyroidism to account for this phenomenon; the observations of Stewart, Deitrick, and Crane[54] point to the absence of this factor in myxedema. There is also evidence for this possibility in the data herein reported. The decrease in peripheral blood flow, in cardiac output, and in the velocity of blood flow after subtotal thyroidectomy demonstrates that operation accomplishes something in the economy of the cardiovascular system which is not achieved by the use of iodine.

SUMMARY

This report concerns studies of the circulation in eighteen patients who were suffering from hyperthyroidism, with special reference to peripheral blood flow. A modification of the method of Hardy and Soderstrom was used to measure peripheral blood flow. The results may be summarized as follows:

1. The peripheral blood flow in c.c./M^2/min. was increased in hyperthyroidism at a time when the basal metabolic rate was elevated, decreased during iodine therapy, with a parallel fall in basal metabolic rate, and decreased still further after subtotal thyroidectomy.

2. There was a linear relationship between peripheral blood flow and basal metabolic rate in hyperthyroidism, in that, "during iodine" and "after operation," the fall in basal metabolic rate was associated with a decrease in peripheral blood flow.

3. In hyperthyroidism the peripheral resistance was low; it increased with iodine therapy, and increased still further after subtotal thyroidectomy. These changes were roughly in inverse ratio to the basal metabolic rate and peripheral blood flow.

4. The cardiac output, in the one case in which it was estimated before treatment, was increased, and showed changes parallel to those in basal metabolic rate and peripheral blood flow in the subsequent periods.

5. Velocity of blood flow, basal metabolic rate, and peripheral blood flow followed the same trend. When the basal metabolic rate and peripheral blood flow were high, the velocity of blood flow was increased. Under iodine therapy and after subtotal thyroidectomy, successive decreases in all occurred.

6. Average skin temperature, measured with a Hardy-Soderstrom radiometer, pulse rate, and pulse pressure followed roughly the fall in basal metabolic rate.

7. No direct relationship was observed between average skin temperature and the temperature of the hand and foot; this was particularly the case with respect to the foot.

PROTOCOLS

Since all of the patients had the typical signs and symptoms of hyperthyroidism, only short protocols are recorded.

M. F., History No. 250693, a white married woman, aged 27 years, was admitted to the hospital Nov. 26, 1939. Clinical diagnosis was diffuse hyperplastic goiter. The cardiac mechanism was normal. At the time of the first measurements, Nov. 27, 1939, "before iodine," the basal metabolic rate was +83 per cent. The administration of Lugol's solution (0.5 Gm., three times daily) was started Nov. 29, 1939. Studies were made "during iodine" on Dec. 14, 1939, when the basal metabolic rate was +45 per cent. Following subtotal thyroidectomy, Dec. 16, 1939, 3 c.c. of Lugol's solution were given by rectum, followed by 0.6 c.c. three times daily by mouth, until Dec. 23, 1939. The basal metabolic rate was +17 per cent when observations were made after operation, Dec. 22, 1939. She was discharged Dec. 24, 1939. The surgical pathologic diagnosis was diffuse hyperplastic goiter, with good involution.

S. K., History No. 229168, a white married woman, aged 41 years, was admitted to the hospital Oct. 17, 1939. Clinical diagnosis was mild, toxic, nodular goiter. The cardiac mechanism was normal. Studies "before iodine" were made Oct. 23, 1939, when the basal metabolic rate was +21 per cent. The administration of syrup of hydriodic acid (0.2 c.c., three times daily) was started Nov. 2, 1939. Measurements were made Nov. 13, 1939, "during iodine" therapy, when the basal metabolic rate was +12 per cent. Following operation, Nov. 18, 1939, she was given 0.3 c.c. of Lugol's solution three times daily until Dec. 1, 1939. When studies were made Dec. 1, 1939, the basal metabolic rate was +3 per cent. She was discharged Dec. 2, 1939. Surgical pathologic diagnosis was adenomatous goiter.

L. G., History No. 252938, a white married woman, aged 40, was admitted to the hospital Dec. 7, 1939. Clinical diagnosis was toxic nodular goiter. Normal sinus mechanism prevailed. Observations were made "before iodine," Dec. 9, 1939, when the basal metabolic rate was +30 per cent. The administration of

Lugol's solution (1.3 c.c. three times daily) was started Dec. 9, 1939. Studies were repeated "during iodine" on Dec. 18, 1939, when the basal metabolic rate was +5 per cent. Subtotal thyroidectomy was performed Dec. 20, 1939, and Lugol's solution was given in doses of 1.3 c.c. three times daily after operation. On Dec. 27, 1939, when measurements were again made, the basal metabolic rate was −1 per cent. Lugol's solution was discontinued, and the patient was discharged the same day. Surgical pathologic diagnosis was fetal adenoma of the thyroid gland.

M. H., History No. 252469, a white unmarried woman, aged 49 years, was admitted to the hospital Dec. 3, 1939. Clinical diagnosis was Graves' disease. The cardiac mechanism was normal. Observations were made "before iodine" on Dec. 12, 1939, when the basal metabolic rate was +47 per cent. The administration of Lugol's solution (0.3 c.c. three times daily) was started Dec. 7, 1939. This was discontinued, and the administration of syrup of hydriodic acid (3 c.c. three times daily) was begun Dec. 15, 1939. On Dec. 30, 1939, measurements were repeated when the basal metabolic rate was +24 per cent. Subtotal thyroidectomy was performed Jan. 6, 1940. Lugol's solution (0.6 c.c. three times daily) was given postoperatively until Jan. 12, 1940. Studies of the peripheral blood flow were made Jan. 12, 1940, when the basal metabolic rate was −1 per cent. She was discharged Jan. 15, 1940. Surgical pathologic diagnosis was diffuse hyperplastic goiter.

M. P., History No. 246435, a white married woman, aged 54 years, was admitted to the hospital Oct. 5, 1939. Clinical diagnosis was toxic nodular goiter. The cardiac mechanism was normal. On Oct. 24, 1939, "before iodine," when the basal metabolic rate was +34 per cent, studies of the circulation were made. The administration of syrup of hydriodic acid (4 c.c. three times daily) was started Oct. 9, 1939. Studies were made on Nov. 8, 1939, "during iodine," when the basal metabolic rate was +24 per cent. Subtotal thyroidectomy was performed Nov. 14, 1939, and the administration of Lugol's solution (1.3 c.c. twice daily) was started. Studies were repeated Nov. 25, 1939, after operation, when the basal metabolic rate had decreased to +17 per cent. Lugol's solution was discontinued Nov. 28, 1939, and the patient was discharged the following day. Surgical pathologic diagnosis was diffuse hyperplastic goiter.

N. L., History No. 213513, a white single woman, aged 18 years, was admitted to the hospital Feb. 10, 1940. Clinical diagnosis was diffuse toxic goiter. The cardiac mechanism was normal. "Before iodine" studies were carried out Feb. 23, 1940, when the basal metabolic rate was +25 per cent. The administration of syrup of hydriodic acid (4 c.c. four times a day) was begun Feb. 22, 1940. Observations were again made during the administration of iodine on March 11, 1940, when the basal metabolic rate was +7 per cent. Lugol's solution (0.6 c.c. three times daily) was substituted for syrup of hydriodic acid on March 12, 1940. Subtotal thyroidectomy was performed March 15, 1940. The administration of Lugol's solution (0.6 c.c. three times daily) was resumed on the first postoperative day and was discontinued March 23, 1940. Studies were made March 23, 1940, when the basal metabolic rate was +2 per cent. She was discharged March 25, 1940. Surgical pathologic diagnosis was diffuse toxic goiter.

C. DiP., History No. 135186, a white single woman, aged 23 years, was admitted to the hospital Feb. 15, 1940. Clinical diagnosis was Graves' disease. The cardiac mechanism was normal. Studies were made on Feb. 28, 1940, "before iodine," when the basal metabolic rate was +53 per cent. The administration of syrup of hydriodic acid (2 c.c. twice daily) was started Feb. 23, 1940, but was replaced by Lugol's solution (0.6 c.c. three times daily) on March 5, 1940. Studies were

made "during iodine" on March 9, 1940, when the basal metabolic rate was +48 per cent. On March 11, 1940, subtotal thyroidectomy was performed and the administration of Lugol's solution (0.6 c.c. three times daily) was resumed; it was discontinued March 15, 1940. Studies "after operation" were made March 18, 1940, when the basal metabolic rate was +17 per cent. She was discharged March 19, 1940. Surgical pathologic diagnosis was diffuse hyperplastic goiter.

P. L., History No. 77117, a white married woman, aged 25 years, was admitted to the hospital May 6, 1940. Clinical diagnosis was diffuse toxic goiter. The cardiac rhythm was normal. Studies "before iodine" were made on May 8, 1940, when the basal metabolic rate was +67 per cent. The administration of Lugol's solution (0.6 c.c. three times daily) was started May 7, 1940. "During iodine," measurements were made on May 23, 1940, when the basal metabolic rate was +38 per cent. Subtotal thyroidectomy was performed May 25, 1940. A single 4-c.c. dose of Lugol's solution in tap water was given per rectum immediately after operation, and the oral administration of Lugol's solution (0.6 c.c. three times daily) was started on the same day and discontinued May 30, 1940. Postoperative measurements were made June 1, 1940, when the basal metabolic rate was +19 per cent. Lugol's solution was discontinued on this day. She was discharged June 2, 1940. Surgical pathologic diagnosis was diffuse hyperplastic goiter.

A. P., History No. 258071, a white married woman, aged 39 years, was admitted to the hospital March 26, 1940. Clinical diagnosis was mild, diffuse, toxic goiter. The cardiac rhythm was normal. Measurements were made "before iodine" on March 20, 1940, when the basal metabolic rate was +21 per cent. The administration of Lugol's solution (0.6 c.c. three times daily) was started March 31, 1940. Studies were carried out "during iodine" on April 9, 1940, when the basal metabolic rate was still +22 per cent. Subtotal thyroidectomy was performed April 12, 1940, after which Lugol's solution (1 c.c. in 1,500 c.c. of saline) was given as an infusion. The oral administration of Lugol's solution (0.6 c.c. three times daily) was started and continued until the day of discharge. "After operation," studies were made on April 20, 1940, when the basal metabolic rate was +6 per cent. She was discharged on April 22, 1940. Surgical pathologic diagnosis was well-involuted hyperplastic goiter.

R. S., History No. 254446, a white single woman, aged 30 years, was admitted to the hospital Jan. 8, 1940. Clinical diagnosis was recurrent Graves' disease. The cardiac rhythm was normal. The first studies were made Jan. 27, 1940, when the basal metabolic rate was +42 per cent. The administration of syrup of hydriodic acid (2 c.c. three times daily) was started Jan. 27, 1940, and replaced by Lugol's solution (1.3 c.c. three times daily) on Feb. 6, 1940. "During iodine," on Feb. 8, 1940, when the basal metabolic rate was +23 per cent, observations were repeated. Subtotal thyroidectomy was done Feb. 17, 1940. The use of Lugol's solution (1.3 c.c. three times daily) was continued. Studies "after operation" were made Feb. 26, 1940, when the basal metabolic rate was +5 per cent. Lugol's solution was discontinued Feb. 27, 1940. She was discharged Feb. 28, 1940. Surgical pathologic diagnosis was diffuse hyperplastic goiter.

M. A., History No. 21804, a white single man, aged 56 years, was admitted to the hospital Nov. 15, 1939. Clinical diagnosis was diffuse toxic goiter. The cardiac rhythm was normal. Studies were made "before iodine" on Nov. 17, 1939, when the basal metabolic rate was +34 per cent. The administration of Lugol's solution (0.6 c.c. three times daily) was started after completing the observations. "During iodine," studies were carried out Nov. 24, 1939, when the basal metabolic rate was +9 per cent. Subtotal thyroidectomy was performed

Dec. 1, 1939. Lugol's solution (0.6 c.c. three times daily) was given until Dec. 5, 1939. Postoperative measurements were made on Dec. 7, 1939, when the basal metabolic rate was –3 per cent. He was discharged Dec. 8, 1939. Surgical pathologic diagnosis was diffuse hyperplastic goiter, with good involution.

M. S., History No. 114675, a white married woman, aged 44 years, was admitted to the hospital Dec. 6, 1939. Clinical diagnosis was toxic nodular goiter. The cardiac mechanism was normal. Studies were made "before iodine" on Dec. 10, 1939, when the basal metabolic rate was +33 per cent. The administration of Lugol's solution (1.3 c.c. three times daily) was started Dec. 9, 1939. Measurements were made "during iodine" on Dec. 26, 1939, when the basal metabolic rate was +11 per cent. On Dec. 28, 1939, subtotal thyroidectomy was performed. The use of Lugol's solution (1.3 c.c. three times daily) was continued until Jan. 6, 1940. Studies were made "after operation" on Jan. 5, 1940, when the basal metabolic rate was +8 per cent. Lugol's solution was discontinued Jan. 5, 1940. The patient was discharged Jan. 6, 1940. Surgical pathologic diagnosis was edematous goiter with fetal embryonal adenoma.

H. M., History No. 247647, a white married woman, aged 30 years, was admitted to the hospital Oct. 30, 1939. Clinical diagnosis was diffuse toxic thyroid. The cardiac rhythm was normal. Measurements were made "before iodine" on Oct. 31, 1939, when the basal metabolic rate was +47 per cent. The administration of Lugol's solution (0.6 c.c. three times daily) was begun Nov. 2, 1939. "During iodine," studies were made Nov. 11, 1939, when the basal metabolic rate was +26 per cent. Subtotal thyroidectomy was performed Nov. 15, 1939, and followed immediately by a single 3-c.c. dose of Lugol's solution, in tap water, by rectum, and 0.6 c.c. three times daily by mouth until Nov. 21, 1939. Measurements were made "after operation" on Nov. 22, 1939, when the basal metabolic rate had fallen to +11 per cent. She was discharged Nov. 22, 1939. Surgical pathologic diagnosis was diffuse toxic goiter showing poor involution.

K. H., History No. 89716, a white widow, aged 41 years, was admitted to the hospital Feb. 6, 1940. Clinical diagnosis was diffuse toxic goiter. The cardiac rhythm was normal. Studies were made "before iodine" Feb. 10, 1940, when the basal metabolic rate was +32 per cent. The administration of syrup of hydriodic acid (4 c.c. four times a day) was started Feb. 11, 1940, but was replaced by Lugol's solution (1.3 c.c. three times daily) Feb. 22, 1940. "During iodine," when the basal metabolic rate was +21 per cent, on Feb. 19, 1940, observations were repeated. Subtotal thyroidectomy was performed Feb. 27, 1940. Lugol's solution (3 c.c., in tap water) was given by rectum immediately after operation, and 4 c.c. in tap water by rectum on the following day. The oral administration of Lugol's solution (1.3 c.c. every four hours) was started Feb. 28, 1940. It was not discontinued until discharge. Postoperative studies were made March 6, 1940, when the basal metabolic rate was +9 per cent. She was discharged March 7, 1940. Surgical pathologic diagnosis was diffuse hyperplastic goiter.

E. B., History No. 263666, a white widow, aged 40 years, was admitted to the hospital April 10, 1940. Clinical diagnosis was diffuse toxic goiter. The cardiac rhythm was normal. When studies were first carried out, on April 12, 1940, "before iodine," the basal metabolic rate was +52 per cent. The administration of syrup of hydriodic acid (4 c.c. four times daily) was started April 15, 1940. Lugol's solution (0.6 c.c. three times daily) replaced this on May 6, 1940. At the time measurements were made "during iodine," on May 4, 1940, the basal metabolic rate was +23 per cent. On May 9, 1940, subtotal thyroidectomy was performed; Lugol's solution (0.6 c.c. three times daily) was continued until May 15, 1940. "After operation," measurements were made May 15, 1940, when the

basal metabolic rate was +13 per cent. She was discharged May 16, 1940. Surgical pathologic diagnosis was diffuse hyperplastic goiter.

E. S., History No. 100740, a white married woman, aged 52 years, was admitted to the hospital Jan. 27, 1940. Clinical diagnosis was diffuse toxic goiter. The cardiac rhythm was normal. The basal metabolic rate, "before iodine," was +58 per cent on Jan. 29, 1940, when observations were made. The administration of Lugol's solution (0.6 c.c. three times daily) was begun Jan. 29, 1940. Measurements were repeated "during iodine" on Feb. 21, 1940, when the basal metabolic rate was +40 per cent. The first stage of a two-stage subtotal thyroidectomy was performed on the right lobe Feb. 27, 1940. The administration of Lugol's solution (0.6 c.c. three times daily) was continued. On the first postoperative day, Feb. 28, 1940, auricular fibrillation occurred. She was digitalized; the rhythm had reverted to normal the next day. Studies of the circulation were carried out March 9, 1940, when the basal metabolic rate was +14 per cent. Removal of the left lobe of the thyroid was carried out March 11, 1940. Lugol's solution (0.6 c.c. three times daily) and digitalis were continued. Studies were made again March 18, 1940, when the basal metabolic rate was +17 per cent. Digitalis was discontinued March 15, 1940, and the auricular fibrillation did not recur. Lugol's solution was discontinued March 17, 1940. She was discharged March 19, 1940. Surgical pathological diagnosis was: right lobe, diffuse hyperplastic goiter; left lobe, diffuse hyperplastic goiter, with chronic strumitis.

A. S.,[I] History No. 230995, a white married woman, aged 41 years, was admitted to the hospital Feb. 27, 1940. Clinical diagnosis was toxic nodular goiter. The cardiac rhythm was normal. In this case the cardiac output was measured, in addition to the other circulatory measurements. "Before iodine," on Feb. 28, 1940, the peripheral blood flow was measured when the basal metabolic rate was +60 per cent. On the following day, when the basal metabolic rate was +54 per cent, the cardiac output was measured. The administration of Lugol's solution (0.6 c.c. three times daily) was started Feb. 29, 1940. "During iodine," measurements of peripheral blood flow were made March 7, 1940, when the basal metabolic rate was +18 per cent. On the next day, when the basal metabolic rate was +15 per cent, the cardiac output was estimated. Subtotal thyroidectomy was carried out March 9, 1940. Lugol's solution (3 c.c., in tap water) was given by rectum immediately after operation, and the oral administration of 0.4 c.c. three times daily was started. On March 10, 1940, Lugol's solution (4 c.c., in tap water) was given by rectum, in addition to that by mouth. Measurements "after operation" were made on March 16, 1940, when the basal metabolic rate was +4 per cent. On the following day, when the basal metabolic rate was −5 per cent, the cardiac output was again measured. Lugol's solution was discontinued March 19, 1940, and she was discharged the next day. Surgical pathologic diagnosis was diffuse hyperplastic goiter.

A. S.,[II] History No. 260735, a white married woman, aged 42 years, was admitted to the hospital March 11, 1940. Clinical diagnosis was Graves' disease. Auricular fibrillation was present. Studies were made "before iodine" on March 16, 1940, when the basal metabolic rate was +52 per cent. After completion of these observations she was given 1.4 Gm. of digitalis on March 16, 0.4 Gm. on March 17, 0.3 Gm. on March 18, and 0.1 Gm. twice daily from March 19, 1940, until operation. A second set of studies "before iodine" was made on March 23, 1940, in order to evaluate the effect of digitalis. The basal metabolic rate, at this time, was +64 per cent. The administration of syrup of hydriodic acid (4 c.c. four times a day) was started March 23, 1940. It was replaced by Lugol's solution (0.6 c.c. three times daily) on April 26, 1940. The basal metabolic rate

was +24 per cent on April 27, 1940, when the peripheral blood flow was measured; at this time the patient was under the influence of digitalis and iodine. Subtotal thyroidectomy was performed May 4, 1940, and Lugol's solution (0.6 c.c. three times daily) was continued. The administration of digitalis (0.1 Gm. twice a day), which had been discontinued after operation, was begun again on May 9, 1940, and continued thereafter. Postoperative measurements were made on May 9, 1940, when the basal metabolic rate was +13 per cent. Lugol's solution was discontinued May 10, 1940. She was discharged May 11, 1940; the auricular fibrillation was still present. Surgical pathologic diagnosis was diffuse hyperplastic goiter.

We wish to thank the members of the Surgical Department of the New York Hospital, whose cooperation enabled us to make observations during the several stages of therapy.

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DISCUSSION

DR. EUGENE F. DuBOIS, New York.—Dr. Stewart and Dr. Evans, under the conditions of their experiments in these studies, have shown that there is a very beautiful parallelism between the basal metabolic rate, peripheral blood flow, and skin temperature. I think it is exceedingly important, however, not to jump to the conclusion that skin temperature is necessarily a good index of peripheral blood flow. It is a good index if the normal relationship is maintained between heat loss by radiation, convection, and vaporization, but, if any of these factors is changed, there may be big discrepancies between surface temperature and peripheral blood flow and heat loss.

We have studied a good many conditions with the respiration calorimeter, and have found that anything that increases vaporization or convection will cause a drop in skin temperature at the time when heat loss and peripheral blood flow are increased.

For example, after exercise the skin temperature goes down markedly because the increased vaporization is cooling the skin at a time when heat loss is increased.

The formula that has been presented seems complicated, but it apparently works out well in the studies that we have made of the direct heat loss in the calorimeter.

I want to emphasize the fact that the authors have studied heat loss, not heat production. There may be big differences when the body temperature is changing. I also want to emphasize the fact that they have studied the surface temperature and the peripheral blood flow of the whole skin, and not simply the hands and feet. The hands and feet represent about 12 per cent of the total surface, and a great many people have neglected the other 88 per cent.

This rather complicated method has been checked in a good many laboratories, and I think is generally accepted. It certainly gives great promise of affording useful information in many conditions other than Graves' disease.

DR. J. MURRAY STEELE, New York.—I should like to ask just two questions. One is, What is the normal value of peripheral blood flow per square centimeter with this method? Why did you discard what I took to be a fall in rectal temperature in both cases? With the known constancy of rectal temperature, a change of a few tenths of a degree may often be more important than one of many degrees in the surface temperature.

DR. DAVID I. ABRAMSON, Cincinnati.—In support of this work, I should like to say that we have used the venous occlusion plethysmographic method in studying the forearm, which we consider a very constant bed, and have found that if a hyperthyroid patient has a basal metabolism of +60 per cent, or so, the blood flow in the forearm will be as high as 6 c.c. per minute per 100 c.c. of limb volume, whereas in a normal person it is about 1 to 2 c.c. Following thyroidectomy, the blood flow returns, within a few days, to the normal level. We have observed this in a number of hyperthyroid cases.

DR. STEWART.—I would like to emphasize one or two points. These measurements afford objective evidence which confirms the clinical impression that the flushed appearance and warm skin of patients with Graves' disease indicate an increase in peripheral blood flow.

The partition of the cardiac output among the various parts of the human body is not known. Blalock has approximated this for certain of the arteries in dogs, but how much of the total output per minute is allocated to the different organs of the human body is not known.

In the first case that Dr. Evans demonstrated, we made measurements of cardiac output at the time that the peripheral blood flow was measured. This patient's total cardiac output was 6 L. per minute, which is a tremendous increase. In terms of liters per square meter, to which the measurements of peripheral blood flow were reduced, the cardiac output amounted, before treatment, to 3.48 L. per square meter per minute (the normal is about 2). At that time, the peripheral blood flow in that patient amounted to 212 c.c. per square meter per minute when the basal metabolic rate was +60 per cent.

After iodine therapy, this value fell to 2.53 L. per square meter per minute, when the blood flow was 125 c.c. and the basal metabolic rate +18 per cent. Then, after operation, the cardiac output fell to 2.02 L. per square meter per minute, which is normal, and the blood flow was 69 c.c. and the basal metabolic rate +6 per cent. Thus, the total cardiac output and the output per unit of body surface area were adequate to divert these added amounts of blood to the skin.

Finally, the further decline in all of the functions which we measured after thyroidectomy demonstrates that operation accomplishes something for cardiovascular system that is not achieved by the use of iodine.

DR. EVANS.—Referring to Dr. Steele's question about the normal values. Hardy and Soderstrom have found that about 0.015 c.c. per square centimeter per minute is the normal volume of blood flow. We have calculated ours in square meters, which would be approximately 15 c.c. per square meter. It must be remembered that that is at the upper limit of our room temperature, and probably decreases to just a few cubic centimeters at a lower room temperature, down to the lower level of the cool zone.

Of several patients with myxedema whom we have studied, whose peripheral blood flow was reduced, one, in particular, had a peripheral blood flow of 8 c.c. at the upper level of room temperature.

In reference to the rectal temperature, it is quite true that, because of the weighting of 80 per cent for the deeper tissues, small variations in rectal temperature may make quite a marked change in the calculated peripheral blood flow. We have found that, in most instances, this is beautifully counterbalanced by the changes in skin temperature; most of them are remarkably constant, with the exception of the first two phases. There is a good deal of vasomotor instability, as you probably observed. In the later phase, after operation, when the vasomotor system seems to cool off, so to speak, these changes compensate one another.

CIRCULATORY REACTIONS IN THE GASTROINTESTINAL TRACT ELICITED BY LOCALIZED CUTANEOUS STIMULATION

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LOCALIZED cutaneous stimulation by means of thermal, mechanical, and chemical agents has long been utilized in the treatment of visceral and other deeply located lesions, but there has been no general agreement regarding the mechanisms through which its beneficial effects are brought about. The assumption that alleviation of pain, by applying heat or other stimulating agents to the skin, is associated with circulatory changes in the diseased area is supported by clinical and experimental data. Certain experimental data also support the assumption that the reflex responses of the musculature of visceral organs which are elicited by localized cutaneous stimulation are accompanied by reflex changes in the tonus and caliber of the blood vessels in question.

Reflex responses of the gastric musculature, including the pyloric sphincter, elicited by warm and cold applications to the skin of the epigastric area have been described in detail by Freude and Ruhmann[1] (1926); their observations were made with the fluoroscope. Comparable reactions of the gastric musculature, according to Ruhmann[2] (1927), may be elicited by appropriate, localized mechanical or chemical stimulation of the skin. Ruhmann also pointed out that the response of the gastric musculature occurs only after a change in the tonic state of the cutaneous blood vessels in the area stimulated has taken place, and that the blood vessels of the stomach undergo a change in tonus corresponding to that of the cutaneous vessels in the area stimulated. These statements are in full accord with certain clinical observations reported by Boas[3] (1926). He noted that warm applications in the epigastric area may cause a peptic ulcer, the existence of which had not been suspected, to bleed. The cessation of bleeding, in cases of bleeding peptic ulcer, effected by cold applications to the epigastrium is undoubtedly the result of vasoconstriction in and about the area of ulceration.

Circulatory responses in other viscera, elicited by localized cutaneous stimulation in appropriate areas, also have been recorded. Freude and Ruhmann[1] produced marked hyperemia of the ascending colon by applying heat to the skin in the lower abdominal area while the colon was exposed during an abdominal operation. Ruhmann[4] (1933) reported that warming the skin of an upper extremity caused a marked increase in the volume of blood circulating in the thoracic viscera. Keep-

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ing the left arm and hand in warm water until the skin became hyperemic resulted, in certain cases, in the relief of coronary vasospasm.

Although localized cutaneous stimulation by means of various agents is widely employed in the treatment of disease, there is no general agreement regarding its therapeutic value, or the manner in which deep lesions, particularly lesions of visceral organs, are influenced by it in cases in which it is beneficial. It has been assumed, without adequate supporting data, that thermal stimulation of the skin by means of warm and cold applications exerts direct thermal effects on the underlying viscera. Even if a direct thermal effect could be demonstrated in cases in which the viscus in question is separated from the area of stimulation only by the thin abdominal wall, it could not be assumed that the stimulus has the same effect when it is applied to the skin of the back or that of an extremity. The assumption that the circulatory changes which are elicited in visceral organs by cutaneous stimulation are reflex phenomena mediated through segmental and intersegmental reflex arcs seems more plausible, and is supported by certain clinical and experimental data.

The present investigation was undertaken to determine more accurately than is indicated by the data hitherto available whether appreciable circulatory changes in visceral organs can be brought about by means of localized cutaneous stimulation, and whether the changes which occur are direct effects of the stimulation employed, or are reflex phenomena.

METHODS

The experiments were carried out on decerebrated cats. Decerebrate preparations were used in order to avoid the vitiating effects of anesthesia. Decerebration was performed with the animal under ether anesthesia, but the stimulation experiments were not begun until the anesthetic effect of the ether and the shock of the operation had subsided.

Warm and cold applications and vacuum cups were employed as stimulating agents; they were applied to the skin of the back and lateral surfaces of the trunk, from which the hair had been removed. The changes brought about in the blood vessels of the stomach and intestine were observed with the viscus exposed through a midventral incision, and were recorded photographically and plethysmographically. In order to ascertain whether the visceral blood vessels could react to cutaneous stimulation in the absence of segmental cutaneovisceral reflex arcs, some of the animals used were subjected to bilateral section of the splanchnic nerves and extirpation of the sympathetic trunks in the lumbar segments before the stimulation experiments were carried out.

EXPERIMENTAL DATA

In all of the decerebrate animals, except those which had been subjected to bilateral section of the splanchnic nerves and extirpation of the lumbar segments of the sympathetic trunks, thermal stimulation and cupping of the skin of the back and lateral body surfaces elicited changes in the blood vessels of the stomach and intestine which were of the same order as those of the cutaneous vessels in the area stimulated. The application of cold packs to the skin of the back or lateral

body surface, from the fifth or sixth thoracic segment caudad, consistently resulted in vasoconstriction in the stomach and intestine. The application of warm packs to the same areas, raising the skin temperature to 45° to 50° C., consistently caused vasodilation in the stomach and intestine. The optimum temperature of warm applications for the production of vasodilatation in the gastrointestinal tract in the cat seems to lie within this range. When packs were applied which were warm enough to raise the local skin temperature to 52° C. or higher, the initial vascular response in the gastrointestinal tract was not vasodilation, but vasoconstriction. Cutaneous stimulation by means of the vacuum cups resulted in vasodilatation in the corresponding portion of the gastrointestinal tract of approximately the same degree as that caused by moderate warming of the skin in the same area.

The changes in the caliber of gastric and intestinal blood vessels brought about by the varieties of cutaneous stimulation which we employed in these experiments became apparent within a few seconds after the application of the stimulus, and reached their maximum within a relatively short interval. This is illustrated most satisfactorily by the plethysmograms which were obtained from loops of the small intestine (Fig. 1). The rise in the tracing caused by local warming of the skin and the fall caused by local cooling of the skin may take place relatively abruptly, as illustrated in the upper part, or more gradually, as illustrated in the lower part of Fig. 1.

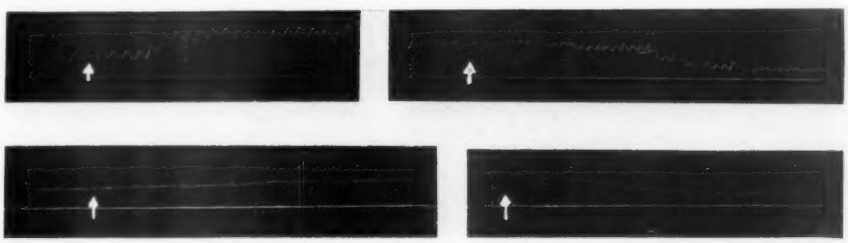

Fig. 1.—Plethysmograms of a loop of the small intestine of the decerebrate cat during localized cutaneous stimulation by means of warm and cold applications. Initiation of stimulation is indicated by arrows. *A*, Response to warm applications; *B*, response to cold applications.

Photographs of segments of the gastrointestinal tract which were obtained during intervals of vasodilatation caused by local warming of the skin and during intervals of vasoconstriction caused by local cooling of the skin, when compared with those which were made when the skin was not being specifically stimulated, indicate that the changes in caliber brought about by this kind of stimulation are more marked in the smaller blood vessels than in the larger ones. Direct observation, with low magnification, also supports this conclusion. When the skin was warmed, the smallest vessels in the affected segments of the gastrointestinal tract which could be seen before the thermal stimulus was applied became more apparent, and many of them could be traced farther than before. Also, many small vessels which could not be seen

before the skin was warmed became visible. Furthermore, increased redness of the viscus indicated that the volume of blood in its capillary bed had increased. When the skin was cooled, many of the smallest vessels in the affected segments of the gastrointestinal tract which could be seen before the cooling became invisible within a few seconds.

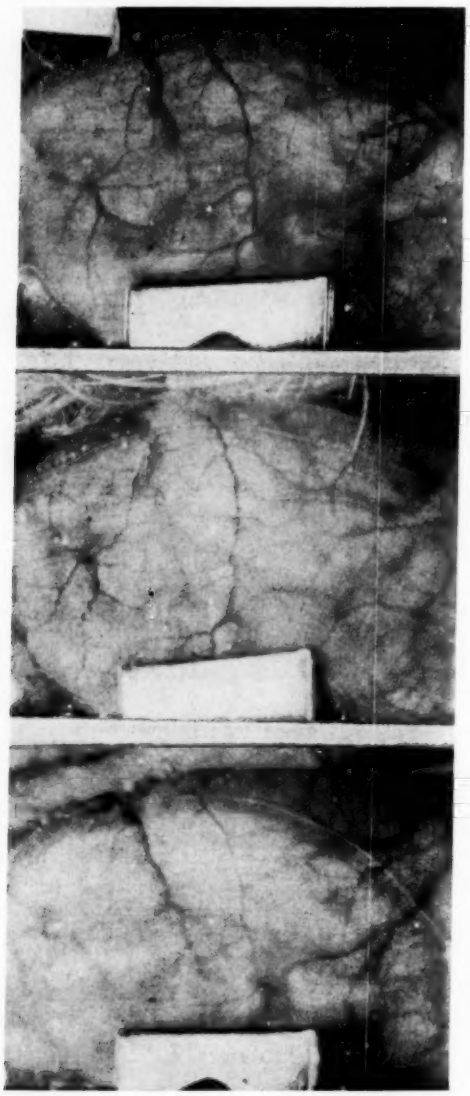

Fig. 2.—Enlarged photographs of a segment of the large intestine of the decerebrate cat, illustrating vascular responses to localized cutaneous stimulation by means of cold and warm applications. *A*, Taken during response to cold application; *B*, taken when no stimulation was being applied; *C*, taken during response to warm application.

Blanching of the viscus in some degree also indicated a decrease in the volume of blood in its capillary bed. In the accompanying photographs (Fig. 2), which have been enlarged, the presence of many small blood vessels during cutaneous stimulation by means of warm applications and the absence of many of the same vessels during cutaneous stimulation by means of cold applications are more significant than the differ-

ences in the caliber of the larger vessels. The caliber changes in the smaller vessels, as shown by a comparison with the photographs which were made when no specific cutaneous stimulation was being applied, are sufficient to warrant the conclusion that the volume of blood circulating through the affected segments of the gastrointestinal tract is markedly increased by local warming and markedly decreased by local cooling of the skin.

The circulatory changes in the gastrointestinal tract which were observed and recorded in our experiments obviously cannot be explained on the assumption that the gastrointestinal blood vessels were influenced directly by the stimulus employed, for the stimulating agent was applied to the skin of the back and lateral surface of the trunk, while the viscus under observation was exposed through a mid-ventral incision in the abdominal wall. The assumption that these circulatory changes were brought about reflexly through segmental and intersegmental reflex arcs which include sympathetic neurons (Fig. 3) is supported by the fact that they failed to appear in decerebrated animals in which the splanchnic nerves had been severed and the lumbar segments of the sympathetic trunks removed. Ruhmann[2] also reported failure to produce circulatory changes in visceral organs by means of localized cutaneous stimulation in human subjects after blocking the sympathetic ganglia through which the viscera in question are innervated.

Reflex vasoconstriction in the gastrointestinal tract, mediated through segmental and intersegmental cutaneovisceral reflex arcs, can be explained satisfactorily, for the sympathetic nerves of the abdominal viscera, components of which constitute the distal units in the efferent limbs of the cutaneovisceral reflex arcs, include vasoconstrictor fibers. The assumption that these nerves also include vasodilator fibers is supported by conclusive experimental data (Burn,[5] 1938). Consequently, reflex vasodilatation in the gastrointestinal tract, mediated through segmental and intersegmental reflex arcs, can also be explained satisfactorily on the basis of available anatomic and physiologic data.

Because of the arrangement of the visceral components of the spinal nerves, cutaneous stimulation in an area which involves but a few segments of the body may evoke reflex vascular responses in a relatively extensive portion of the gastrointestinal tract. The somatic rami of the spinal nerves are arranged segmentally, although the areas of distribution of adjacent spinal nerves overlap to some extent; but the efferent components of the visceral rami of these nerves effect synaptic connections with sympathetic ganglion cells, the distribution of whose axons is not limited to a single segment and parts of the adjacent ones. The blood vessels in a relatively long segment of the gastrointestinal tract, consequently, may be influenced by impulses conducted through the visceral efferent components of a single spinal nerve.

The observation recorded above, that, as a result of cutaneous stimulation, the smaller vessels in the gastrointestinal tract undergo more

marked changes in caliber than the larger ones, is in full accord with the opinion of Burn,[5] based on his own experience and an exhaustive review of the literature, that the sympathetic vasodilator fibers innervate the peripheral branches of the intestinal arteries. Therefore, dilatation of the terminal arterial branches, including the arterioles and the capillary bed, may facilitate the flow of blood through the organ, while the general blood pressure is safeguarded by the tonicity of the larger arteries.

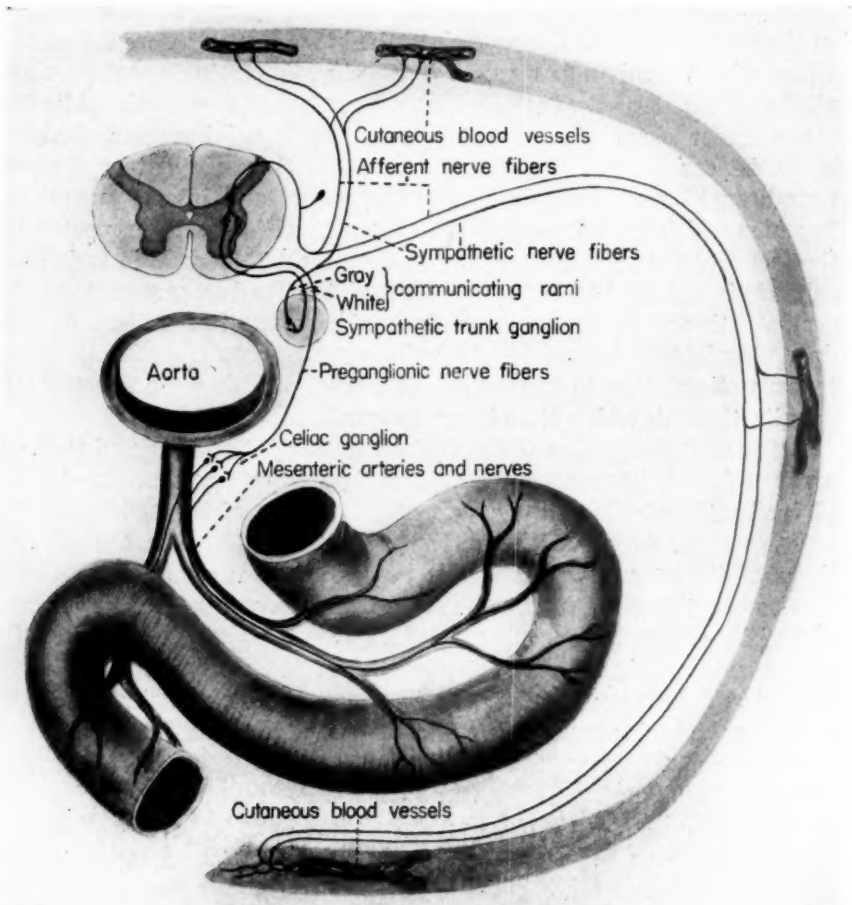

Fig. 3.—Diagrammatic illustration of cutaneovisceral vasomotor reflex arcs.

In all of our experiments in which the application of warm packs or the alternate application of warm and cold packs in the same cutaneous area was prolonged, the skin in this area became markedly hyperemic. The localized cutaneous hyperemia produced in this manner persisted for some time after removal of the stimulating agents. During this interval, cooling of the skin in the hyperemic area did not result in vasoconstriction in the gastrointestinal tract, nor did the further use

of warm applications result in increased vasodilatation in the viscus. This is in full accord with the observation reported by Ruhmann,[4] namely, that the gastrointestinal musculature does not respond reflexly to local warming of the skin until dilatation of the cutaneous blood vessels in the area stimulated has taken place. These observations support the assumption that stimulation of the receptors involved in cutaneovisceral vasomotor reflexes is associated with changes in the tonic state of the cutaneous blood vessels.

SUMMARY AND CONCLUSIONS

In this series of experiments, circulatory changes in the gastrointestinal tract were produced by localized stimulation of the skin. The changes in the caliber of the gastrointestinal vessels which were observed and recorded corresponded to those produced in the cutaneous vessels in the area stimulated. Moderate, localized warming of the skin (to 45° to 50° C.) and the application of vacuum cups produced vasodilatation in the cutaneous area stimulated and in the corresponding segments of the gastrointestinal tract. Localized warming of the skin to 52° C., or more, caused initial vasoconstriction in the gastrointestinal tract. Moderate, localized cooling of the skin resulted in vasoconstriction in the cutaneous area stimulated and in the corresponding segments of the gastrointestinal tract. The caliber changes in the gastrointestinal blood vessels were more marked in the smaller ones than in the larger.

The vasoconstriction and the vasodilatation in the corresponding portions of the gastrointestinal tract which were brought about by the use of cold and warm applications, respectively, were sufficiently marked to warrant the conclusion that the volume of blood flowing through the affected segments of this viscus is markedly decreased by local cooling and markedly increased by local warming of the skin.

The circulatory changes in the viscera which are produced by localized cutaneous stimulation can be explained most satisfactorily as reflex reactions mediated through segmental and intersegmental cutaneovisceral reflex arcs. Stimulation of the receptors involved in these reflex reactions is probably associated with a change in the tonic state of the cutaneous blood vessels in the area in question.

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APPLICATIONS OF PHOTOELECTRIC PLETHYSMOGRAPHY IN PERIPHERAL VASCULAR DISEASE*†‡

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THE great interest in the peripheral circulation in recent years led to the development of many observational methods and their application to the study of physiologic and clinical problems in this field. These methods use changes in skin temperature, in color and volume of the part, in electrical conductivity, in thermal conductivity, in heat radiation and heat loss, in insensible perspiration, and in arteriovenous oxygen differences as criteria of the blood flow and the state of the blood vessels in the observed part. No one of these methods permits a direct record of blood flow, although the results obtained by all of them agree, under circumstances suitable for their individual application, as to the qualitative character of the changes in blood flow. The addition of other observational techniques renders a service if they possess any advantages in application over previous methods.

The photoelectric plethysmograph has been intensively studied and extensively applied in this laboratory.[1-5] Our experiences in using this method on patients have proved profitable in its refinement and evaluation as a clinically useful tool. Some of these data are detailed here in order to direct attention to the advantages of the method.

METHOD

The essentials of, and the sources of error in, photoelectric plethysmography have been described in other communications.[1-5] Certain refinements and conveniences in the construction and application of the plethysmograph, and in recording, may be added here. Fig. 1 shows the present form of the plethysmograph for exploring the vasculature of various skin areas. When prolonged, continuous observations are desired on the fingers or toes, it is convenient and preferable to attach a thin copper shelf for the digit to rest on. Wrapping the copper sheet about the digit helps greatly to secure proper immobilization, but one must avoid any pressure on the digit. It is still better to prepare an *incomplete* plaster of Paris cast of the digit when it is in position in the copper trough of the plethysmograph. This secures complete immobilization without any interference with the blood supply, but one must wait for the cast to dry before using it, for temporary local vascular disturbances result from the temperature changes induced by the drying of the cast.

The best way to apply the plethysmograph to the skin of the head, to the ear, or to the nasal septum is to suspend it from a plaster of Paris cast of the cranium which rests on the head of the subject (Fig. 2). This cast is prepared in advance by covering the hair with a bathing cap (which is later removed), and then apply-

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ing plaster of Paris bandages until a sufficiently rugged cast results. As the bandage strip is wrapped on, a small brass plate, carrying a screw, is set in the bandage. The screw later receives a ball for a ball-and-socket joint, which affords a convenient means of adjusting the plethysmograph to varying skin contours. This arrangement has very important advantages from the viewpoint of rigidity of support of the plethysmograph and the comfort of the subject. The cast, since it is individually fitted, uniformly distributes the weight over the entire head, and so avoids local pressure, which may become extremely distressing. Subjects have carried several plethysmographs on such a cast for several hours without discomfort and have even fallen asleep during observations.

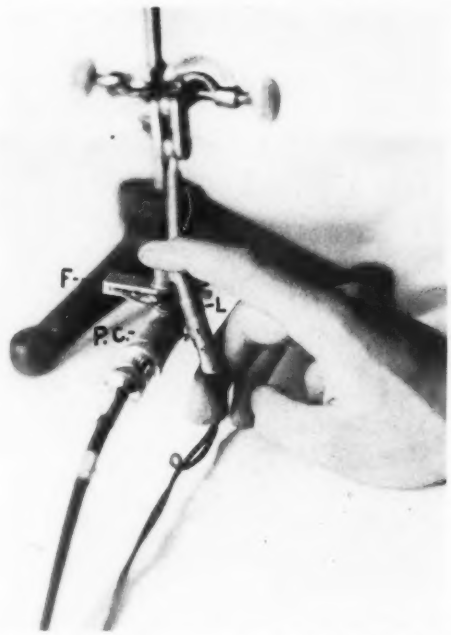

Fig. 1.—The photoelectric plethysmograph. *P. C.*, Photoelectric cell in housing. *L.*, Pencil flashlight bulb, mounted on carrier. The bulb is actually inside the brass tube, about 5 mm. from the skin surface. *F.*, Filter carrier, with small round disc of glass serving as filter.

Recording may be done with high frequency instruments, such as the string galvanometer, but their only advantage is for wave form analysis. They are not necessary for routine plethysmography, for which we use modified milliammeters. The pointer of the meter is bent so that its end rotates in the axis of rotation of the coil. A small mirror mounted on the end of the pointer provides for photographic recording. (We owe this suggestion to Doctor Con Fenning, of the University of Utah.) The records so obtained are quite suitable for estimating the arterial supply, using the "filter" technique.[1] Comparison of the amplitude of the oscillations so recorded and also simultaneously recorded with a high frequency instrument shows that little error is introduced by substituting the inexpensive milliammeters, which have the added advantage of being insensitive to alternating current oscillations.

Illumination of the skin area is provided by a pencil-type flashlight bulb. This type of bulb, with its "drop" lens, provides a concentrated light sufficiently strong for the purpose. Stronger lights give rise to local heating effects. Even these small bulbs will gradually raise the temperature (as measured by a thermocouple) when the blood supply is normal, but in ischemic skin this effect develops

so slowly that estimations of blood supply, which can be made immediately after turning on the light, are not affected. The bulbs may be operated either on direct current (dry cells, or, preferably, a storage battery) or, when milliammeters are used for recording, on alternating current. When the latter is used, a voltage regulator is absolutely essential, for, otherwise, the fluctuations in line voltage caused by varying illumination will produce gross distortions in the record.

The photoelectric cell is most conveniently mounted in a microphone connector, in which the female element is placed in the male carrier or cap. Since this cap comes provided with a guide pin, a slot may be cut in the plethysmograph to receive the pin. This provides for swift, accurate, and rigid placement of the photoelectric cell in the plethysmograph, and for convenient removal of the cell when it is necessary to replace it or guard against breakage.

Fig. 2.—The photoelectric plethysmographs mounted on a plaster of Paris cast for simultaneous recording of vascular reactions in skin of the forehead and ear.

PHOTOELECTRIC PLETHYSMOGRAPHY IN THE STUDY OF VASCULAR REACTIONS

The value of photoelectric plethysmography as a control in surgery of the sympathetic nervous system is indicated in Fig. 3, in which the pronounced vasoconstrictor reflex in the finger in response to a deep breath is compared with the extremely small effect in the toe of an epileptic subject on whom a lumbar sympathectomy had been done. The completeness of the denervation of the toe is indicated by the almost total absence of vasoconstrictive reactions, whereas in the finger there are a decisively decreased volume and volume pulse. The innervated toe

usually gives as strong a response to this stimulus as the finger. Smithwick[6] has apparently made a similar application of the photoelectric plethysmograph. Since changes in volume may occur independently of variations in arterial tone,[5] the changes in the volume pulse may be recorded as described elsewhere,[5] in order to follow the changes in arterial tone alone.

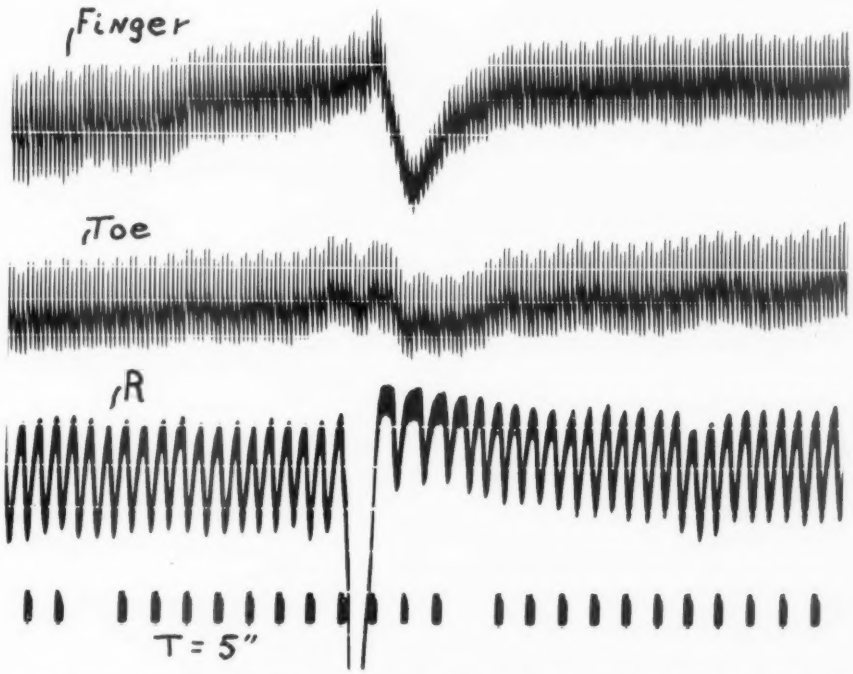

Fig. 3.—Photoelectric plethysmograms of the finger (upper record) and toe (lower plethysmogram) in a case of epilepsy, after lumbar sympathectomy. Deep breath, as indicated on the respiration record. Time: 5 seconds.

The observation of spontaneous activity of the digital arteries by means of the photoelectric plethysmograph (Fig. 4*A*) is particularly interesting in cases of Raynaud's disease (Fig. 4*B*). This patient (a woman, 70 years old, whose blood pressure was 140/95) had Raynaud's syndrome in both hands, the toes, and lips. The figure records activity in the finger pads of the right middle and little fingers. The latter's blood supply, as measured by the "filter" technique (see below), was nearly normal, while the middle finger had a very poor supply. The differences in spontaneous activity of the vessels of the two fingers were quite striking, particularly when compared with the uniformity in spontaneous activity usually exhibited simultaneously by all of the finger arteries in normal subjects (Fig. 4*A*). A similar independence in the activity of the arteries of the middle fingers of the two hands was observed. Both of these fingers had about an equally poor blood supply. Although it is theoretically possible that such independence in activity

depends on innervation, it seems more probable that it resides in peculiarities in the smooth muscle. A suggestion of independence in activity occurs only occasionally in normal subjects. These phenomena are best explained by Lewis' local fault concept.[7]

MEASUREMENT OF THE SKIN BLOOD SUPPLY WITH THE PHOTOELECTRIC PLETHYSMOGRAPH

Securing objective data concerning the blood supply of various skin areas in relation to vascular disorders and the effects of therapy on these disorders is one of the useful applications of this instrument. The principle of the photoelectric method depends on the estimation of the amplitude of the volume pulse in the observed area; this is used as a measure of arterial flow. This relation has been discussed elsewhere.[1] The method has certain advantages over mechanical plethysmographs, namely, speed, extreme sensitivity, convenience, and applicability to areas which cannot be explored by the mechanical plethysmograph.

One proceeds as follows: The plethysmograph is brought into contact with the skin area. The volume pulse is then recorded (Fig. 5). The record is then calibrated in arbitrary units (whose blood equivalent has been discussed elsewhere[1]). The "filter," which is simply a thin sheet of uncolored glass about .042 inch thick (thin microscope slide glass serves), is swung into place between the photocell and the transilluminated skin. This results in the absorption of a constant *fraction* (not a constant amount) of the light reaching the photocell, and so automatically calibrates the intensity of the illumination and the amount of amplification. The deflection in the record so produced is then compared with that of the volume pulse. The amplitude of the volume pulse (measured in mm. at arrow) is then divided by the deflection caused by the "filter" (also measured in mm.). The result is the amplitude of the volume pulse expressed in "filter units." (An error in the measurement of the volume pulse should be pointed out. Either it must be measured always on the same side of the light beam or shadow, or a correction for the width of the beam must be made. This error increases relatively as the volume pulse decreases in recorded amplitude.) When the string galvanometer is used to record the volume pulse on narrow paper, the string is shunted by high resistance during the recording of the volume pulse and by lower resistance during the "filter" deflection. This is necessary in order to secure adequate amplitude of the volume pulse for measurement. The error introduced by the string shunt is ignored, for this is a constant error which does not influence comparisons. The data below and in Fig. 5 were so obtained.

It is necessary to point out that grossly altered dynamics of the heartbeat or of the large arteries will affect the dependability of the volume pulses in skin areas as criteria of the flow through these areas, and of the state of constriction or dilatation of the small arteries and arterioles involved. This source of error is illustrated in cases of patent ductus arteriosis, in which there is a very large pulse pressure. The extraordinarily large volume pulses in these patients' fingers do not appear to represent a correspondingly large blood flow in the fingers, but rather are the result of the large pulse pressure.

The data in Fig. 5 were obtained in a case of Raynaud's disease. The reduction in skin blood supply, as compared with normal values,[1] is evident. These values were obtained one week after right-sided cervical sympathectomy (involving ganglionectomy), when the condition

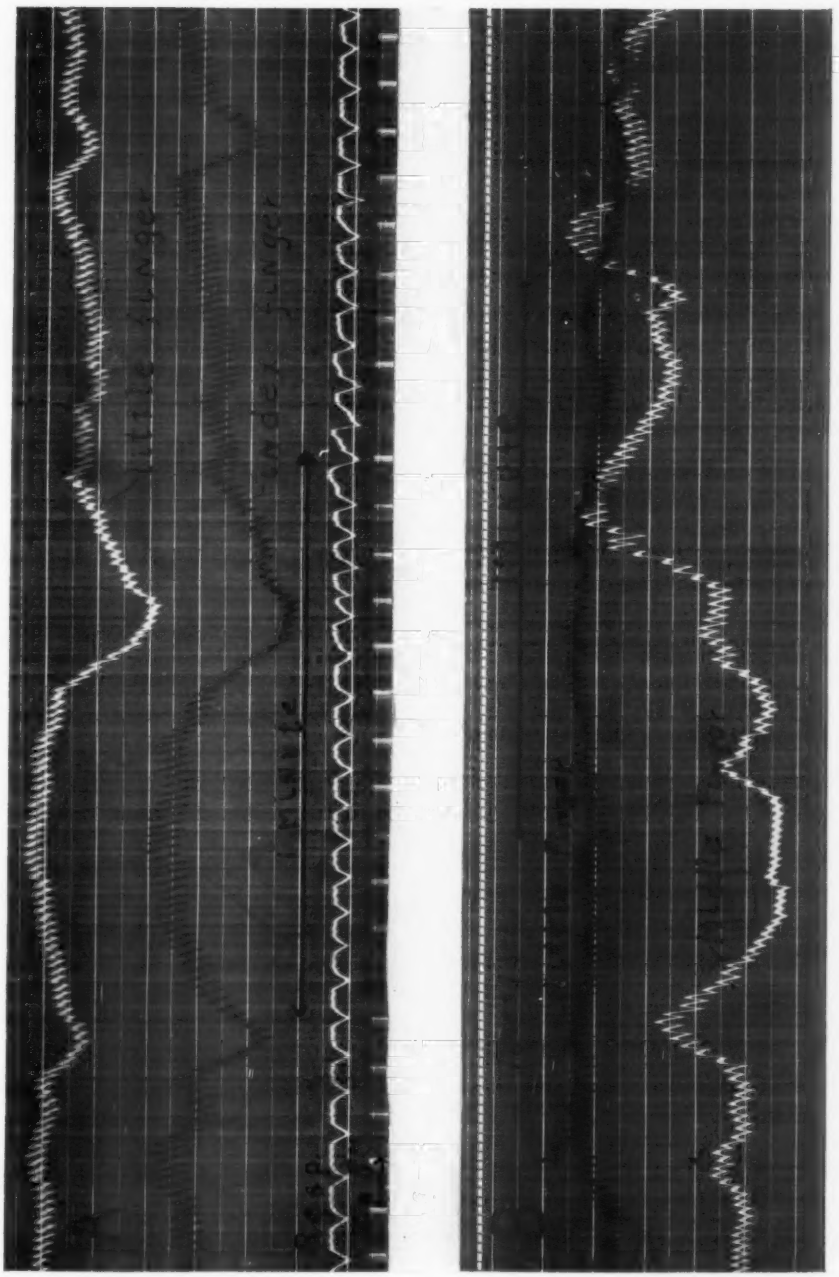

Fig. 4.—Photoelectric plethysmograms of finger pads. *A*, Normal subject; two fingers of same hand; spontaneous waves. *B*, Raynaud's disease; little and middle fingers of right hand; spontaneous waves.

of the patient was poor. The cutaneous ischemia, which was not limited to the right side, was probably the result of a general postoperative impairment of the circulation. This phenomenon is more clearly indicated in Table I. The ability of the plethysmograph to follow the changes

TABLE I

SKIN AREA	11/23/38 78° F.	12/2/38 80° F.	3/4/39 80° F.
Right Hand:			
Index finger	0.58	0.28	0.13
Middle finger	0.73	0.46	0.12
Ring finger	0.67	0.59	0.13
Little finger	0.15	0.0	0.0
Thumb	0.20	0.35	0.23
Left Hand:			
Index finger	0.83	0.12	0.62
Middle finger	1.55	0.28	1.00
Ring finger	0.80	0.21	1.4
Little finger	1.0	0.36	1.7
Thumb	0.73	0.19	1.2
Forehead (right)	0.80	0.31	0.63
Forehead (left)	0.80	0.31	0.80
Nose (right)	0.70	0.45	0.55
Nose (left)	1.00	0.45	1.2

Table I.—Blood supply, as judged by the amplitude of the volume pulses of the pads of the fingers and of the skin of the forehead and nose before and after right-sided cervical sympathectomy. Raynaud's disease. Operation on Nov. 25, 1938. Patient in weakened condition on Dec. 2, 1938. Note the decreased blood supply to all areas on this date. Volume pulses are expressed in "filter" units.

in the skin circulation caused by sympathectomy is well illustrated in this case. Four months after operation, the skin blood supply was reduced on the right side, as compared with the preoperative level. It is interesting to note that this effect likewise occurred on the forehead and nose, although it was less marked here. The instrumental evaluation of the results of interrupting the postganglionic fibers agreed with the clinical impression that the circulation was impaired in the areas affected by the operation. The completeness of the sympathectomy was apparent from the results of applying suitable vasoconstrictor stimuli, such as immersing the opposite hand in ice water (Fig. 6). No reflex constriction occurred in the sympathectomized hand. In contrast, immersion of the right hand in ice water elicited the usual reflex constriction in the opposite hand, whose sympathetic innervation was still intact. In such experiments, arterial constriction is indicated by the decrease in the volume pulse, as well as by the decrease in volume which is caused by the diminished engorgement of all vessels in the pad as a result of decreased flow, which, in turn, is the result of the arterial constriction.[5] No change in volume or volume pulse occurred on the sympathectomized side when vasoconstrictor stimuli were applied. Since the denervated side did not respond, there was no evidence of a secretion of adrenalin in response to the cold stimulus, although current theory postulates an increased sensitivity of sympathectomized extremities to circulating adrenalin.

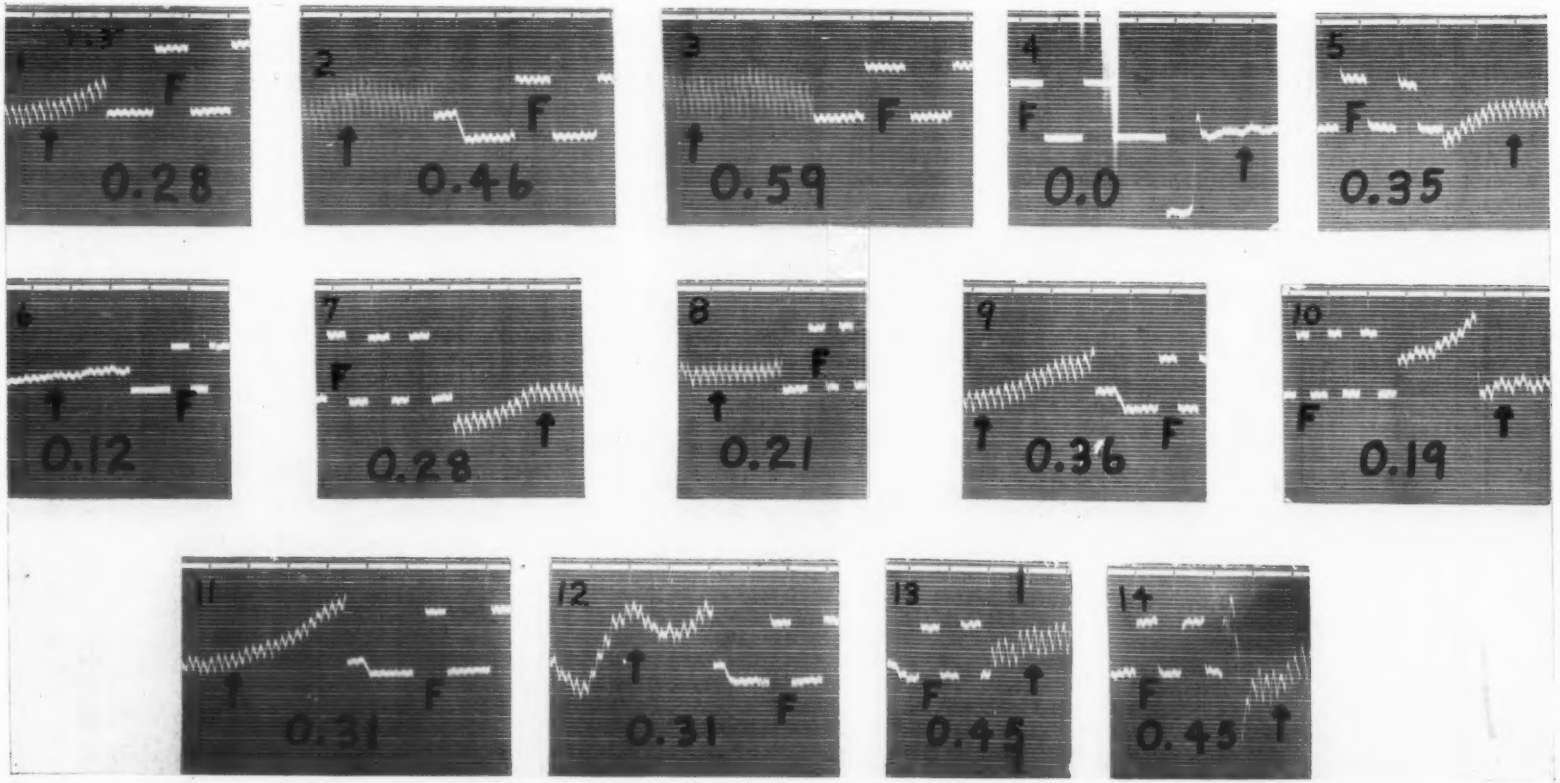

Fig. 5.—The photoelectrically recorded volume pulses in the various skin areas in a case of Raynaud's disease. Filter deflections at *F* and volume pulse measurements at the arrow. Filter equivalent of the volume pulse is written on each record. Upper row: pads of following fingers of right hand: *1*-index, *2*-middle, *3*-ring, *4*-little, *5*-thumb. Middle row: pads of following fingers of left hand: *6*-index, *7*-middle, *8*-ring, *9*-little, *10*-thumb. Lower row: skin of following: *11*-right forehead, *12*-left forehead, *13*-right nose, *14*-left nose.

A case of intermittent claudication, involving both legs, is presented in Table II. These data were obtained in late winter and early spring.

TABLE II

	2/15 26° C.	2/22(2) 26° C.	2/22(3)	3/1 24° C.	3/15 24° C.	3/29(1) 28° C.
Right hand:						
Index finger	1.5	.67			1.0	
Middle finger	1.6	.89			2.0	
Ring finger	1.5	1.0			1.0	
Little finger	1.9	.65			1.0	
Thumb	1.3	.64			1.0	
Right foot:						
Big toe	.2	.2	.0	.3	.04	.75
Second toe	.3	.0	.16	.0	.06	.8
Third toe	.16	.14	.18	.41	.04	.75
Fourth toe	.25	.39	.51	.15	.08	.8
Fifth toe	.27	.22	.15	.18	.04	1.4
Dorsalis pedis	.0	.33	.11	--	.05	.53
Left foot:						
Big toe	.0	.0	.13	.1	.0	.28
Second toe	.21	.0	.0	.1	.0	.28
Third toe	.27	.0	.2	.0	.02	.37
Fourth toe	.2	.13	.2	.15	.05	.33
Fifth toe	.0	.17	.2	.1	.06	.5
Dorsalis pedis	.12	.15	.0	--	.0	.37

(1) Preceded by one week of warm weather. (2) Came from treatment in doctor's office. (3) One hour later.

Table II.—The arterial blood supply of the finger and toe pads, as indicated by the volume pulse amplitude in a case of intermittent claudication involving both thighs. The amplitude of the volume pulse is expressed in "filter" units. Male, aged 63; arteriosclerosis; blood pressure 150/105; dorsalis pedis pulse not palpable.

The subject rested in the laboratory for one hour preceding the determinations, except for the first (Feb. 22), which were made immediately after he arrived in the laboratory, and about thirty minutes after he had been treated with mecholyl iontophoresis. The continuation of poor blood supply to the toes despite treatment is in striking contrast to the effects of a week of warm weather preceding the last group of determinations (March 29). The greater response of the toe pads of the right foot agreed with the clinical impression that the circulation was better on this side. Intermittent venous occlusion was tried on this patient during one of his visits to the laboratory. The results were inconclusive (Table III), with the exception of the pulsations in the dorsalis pedis, which became detectable but were still very small. The changes in the toes were too small to be of any significance.

Mecholyl iontophoresis was tried in this case in the laboratory, fortunately at a time when the volume pulses in the toes were almost indetectable (Table IV). Iontophoresis was administered to both feet and calves. Conditions were ideal for demonstrating a dilator response. Some improvement in the right foot was shown by the increased volume pulse, but the changes in the left foot were too small to have any significance. Histamine iontophoresis in the laboratory, after a week of warm weather, increased the amplitudes of the volume pulses several times in the toes of the left foot, but the results on the right foot were

inconclusive, possibly because the toe vessels on this side were already considerably dilated. We do not know whether this was the maximal dilatation possible.

These therapeutic experiments are presented for their illustrative value, rather than as evidence of the efficacy of iontophoresis or of intermittent venous occlusion. It is obvious, however, that climate did more to open this patient's toe vessels than did the therapy. The experiments demonstrate that the method is capable of providing objective evidence concerning the state of the cutaneous circulation in patients, and is useful in estimating the immediate as well as the delayed effects of therapeutic procedures on the circulation in the treated areas.

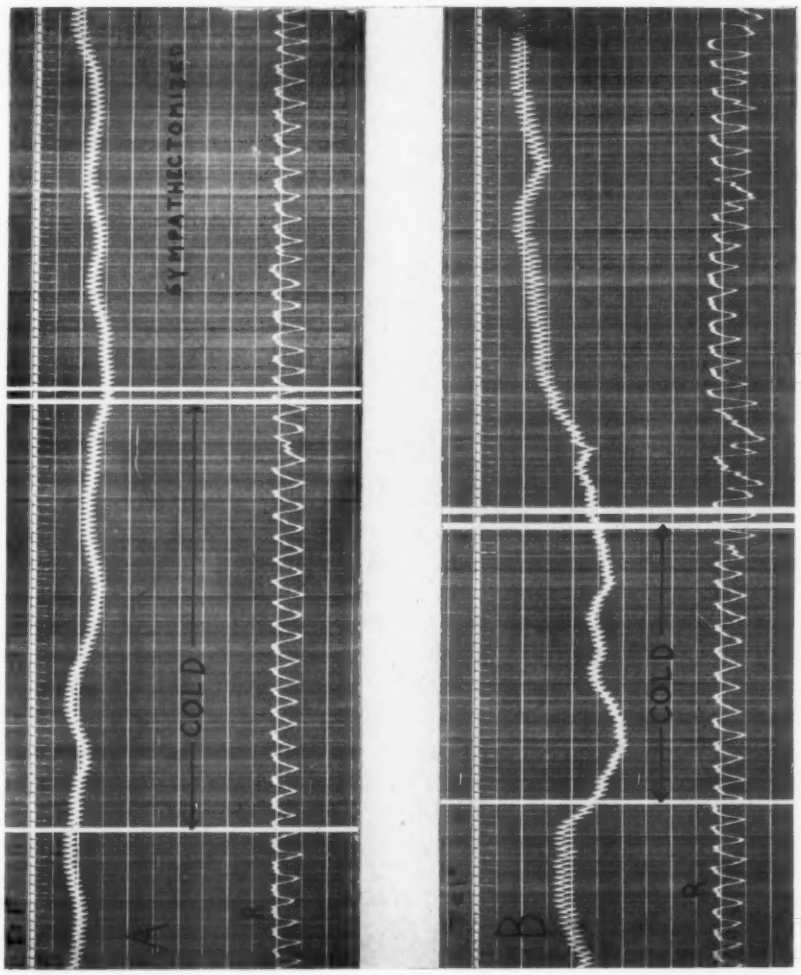

Fig. 6.—Reflex finger responses in a case of Raynaud's disease to cold stimuli applied to the opposite hand. *A*, response of sympathectomized finger. *B*, response of innervated finger. Immersion of opposite hand in ice water between vertical signals. Time: one second. Respiration by pneumograph.

This paper presents the applications of the photoelectric plethysmograph to the study of peripheral arterial reactions and to the estimation of the effects of various therapeutic procedures on the blood supply of

TABLE III

	2:00 to 2:15 23.8° C.	3:30 to 3:40 24° C.
Left foot:		
Big toe	.1	.1
Second toe	.1	.0
Third toe	.0	.13
Fourth toe	.15	.16
Little toe	.1	.2
Dorsalis pedis	.0	.1
Right foot:		
Big toe	.3	.2
Second toe	.0	.2
Third toe	.41	.2
Fourth toe	.15	.2
Little toe	.18	.26
Dorsalis pedis	.0	.14

Table III.—Effect of intermittent venous occlusion on the blood supply of the toes, as judged by the amplitude of the volume pulses (same patient as in Table II). Intermittent occlusion from 2:30 P.M. to 3:10 P.M.

TABLE IV

TIME	RIGHT FOOT						LEFT FOOT					
	BIG TOE	2ND TOE	3RD TOE	4TH TOE	5TH TOE	DORSALIS PEDIS	BIG TOE	2ND TOE	3RD TOE	4TH TOE	5TH TOE	DORSALIS PEDIS
1:50	.05	.06	.04	.08	.04	.0						
2:05							.0	.0	.02	.05	.07	.0
2:50	.14											
3:00	.19											
3:05	.27											
3:10	.25											
3:17	.38											
3:25-3:29	.27	.15	.22	.22	.42							
3:31-3:35							.0	.02	.03	.1	.1	
3:45						.13						.01

Table IV.—Effect of mecholyl iontophoresis to both legs and feet on the blood supply, as judged by the amplitude of the volume pulses of the toe pads (same patient as in Table II). Iontophoresis from 2:50 P.M. to 3:40 P.M.

the skin. The possibilities of this plethysmograph are not thereby exhausted. Its usefulness in distinguishing "active" from "passive" components and in separating arterial from venous reactions in the skin is described in another publication.[5] Under suitable circumstances, in which certain dynamic requirements are met, it appears to be possible to separate arterial reactions, venous reactions, and changes in flow in a skin area by means of the photoelectric plethysmograph. The possible application of this method to the study of disease is being investigated.

SUMMARY

The clinical application of photoelectric plethysmography is described. Its use in following vascular reactions, such as the spastic phenomena of Raynaud's disease, or in evaluating the completeness of sympathetic denervation of the skin, is indicated by selected examples. Its use in estimating the arterial blood supply of the skin of various areas is

illustrated on a normal subject, on a patient after sympathectomy, and after treatment with intermittent venous occlusion and iontophoresis in a case of intermittent claudication.

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Department of Clinical Reports

UNUSUAL CONFIGURATION OF THE HEART IN A CHILD

A. Gerson Hollander, M.D., and J. Hamilton Crawford, M.D.
Brooklyn, N. Y.

THE common causes of abnormalities in the contour of the heart in children are congenital defects and rheumatic heart disease. As a result of the extensive studies which have been made, the nature of these changes is now fairly well understood. Rheumatic lesions can be diagnosed practically with certainty, and a reasonable assumption can be made in the commoner types of congenital abnormality. In the case described below there was an unusual, localized bulge on the left side of the heart. Its situation did not correspond to that of the changes in contour which are present in either of the above-named conditions.

CASE REPORT

A. J., a 13-year-old colored girl, was admitted to the Cardiac Clinic of the Kings County Hospital in January, 1938, with the chief complaint of palpitation and cough on exertion.

The previous history was irrelevant. She was born in Georgia, came to New York City at an early age, and, except for measles and pertussis, neither of which was severe, and occasional sore throats, had had no previous illness. The diet had been adequate and she was alert. There was no history of syphilis in the parents or child. There had been no genitourinary or gastrointestinal complaints, and there was no history of surgical or traumatic disease.

The present illness had commenced six months earlier, when she suffered from tonsillitis, and a nonproductive cough developed. There had been no elevation of temperature at any time. Since then she had had a slight hacking cough, but no fever, night sweats, weight loss, anorexia, posterior nasal discharge, or headache.

Physical examination revealed a well-nourished, well-developed 13-year-old negress, not acutely ill. There was no dyspnea, edema, cyanosis, or clubbing of the fingers. The pupils were equal and reacted to light and in accommodation. The ocular movements were normal, and the conjunctivae were free from icterus and petechiae. The fundi of the eyes were normal. Tonsillar tabs were present in the pharynx. The neck veins were not distended, and there were no palpable lymph nodes in the neck. The pulse rate was 96 and the blood pressure 132/92. The cardiac mechanism was normal. Examination of the heart revealed a marked, visible pulsation over the lower portion of the precordium, between the sternum and the nipple. The apex was palpated 11.5 cm. to the left of the midsternal line in the fifth intercostal space, outside the midclavicular line. No thrill was felt. At the apex a soft systolic murmur, transmitted to the axilla, was heard. This was constant on change of position, and extended throughout most of systole. With the heartbeat there was a clicking sound (like râles) in the region of the apex which extended to the midaxillary line. This was heard best with the patient in the recumbent position. The sounds at the base of the heart were of good quality, and the

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aortic second sound was equal in intensity to the pulmonic second. The lungs were negative on physical examination, as was the abdomen.

Laboratory Examination.—The blood Wassermann reaction was negative. The urea nitrogen content of the blood was 27 mg. per cent, the creatinine, 1.2 mg. per cent, and the sugar, 120 mg. per cent. The specific gravity of the urine was 1.025; the urine contained no albumin, sugar, or acetone, and was negative microscopically. The hemoglobin was 85 per cent, the erythrocyte count, 5,700,000, and the leucocyte count, 5,500; the differential leucocyte count showed 64 per cent polymorphonuclear leucocytes, 34 per cent lymphocytes, and 2 per cent monocytes.

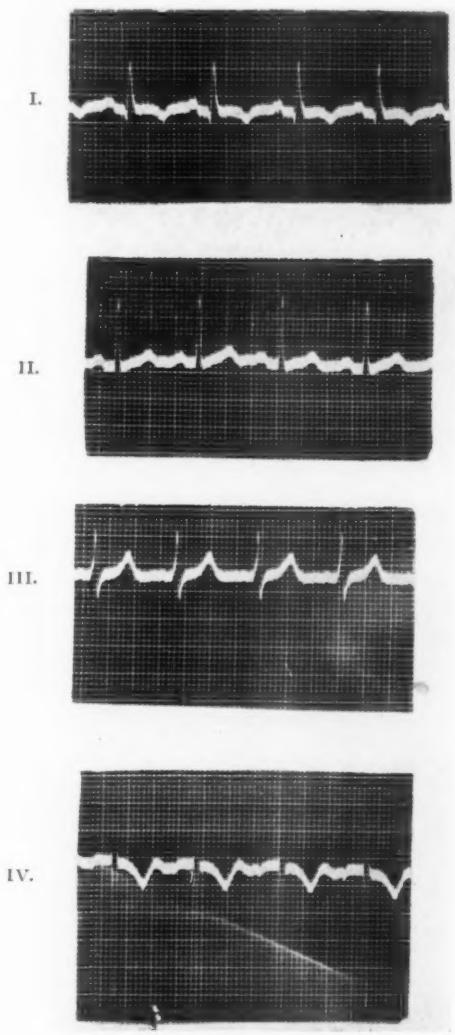

Fig. 1.—Electrocardiogram.

The electrocardiogram (Fig. 1) showed normal cardiac mechanism, a rate of 94, a P-R interval of 0.18 second, and a QRS of 0.08 second. The T wave was moderately inverted in Lead I. Leads II and III were normal. In Lead IV (method of Wolferth and Wood, right arm wire connected to precordial electrode, left leg wire to left leg electrode), the R wave was practically absent.

The teleroentgenogram (posteroanterior) showed a localized bulge at about the mid-portion of the left border of the heart (Fig. 2). In the right anterior oblique position (Fig. 3) the esophagram was normal, and the bulge was seen to protrude beyond the spinal column. The roentgenkymogram (Fig. 4) showed reversal of pulsation over the area of localized enlargement; this portion expanded when the rest of the ventricle contracted.

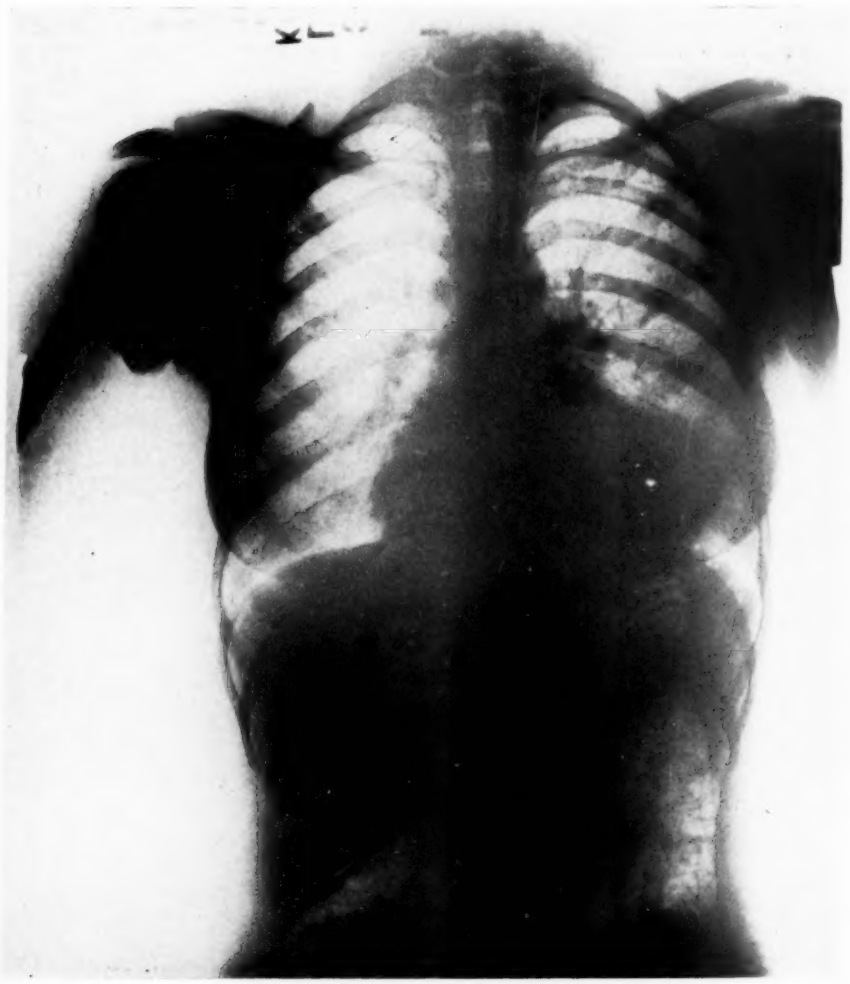

Fig. 2.—Teleroentgenogram (posteroanterior).

DISCUSSION

The outstanding features of this case were the protrusion of the left border of the heart, which showed reversal of pulsation in the roentgenkymogram; a diffuse, visible pulsation between the apex and the sternum; a systolic murmur at the apex, and, distinct from this, but in the same area, a clicking sound which was synchronous with the heartbeat.

The localized bulge in the left border of the heart suggested the following possibilities: (1) tumor of the heart, (2) diverticulum or congenital defect of the pericardium, and (3) aneurysm of the heart.

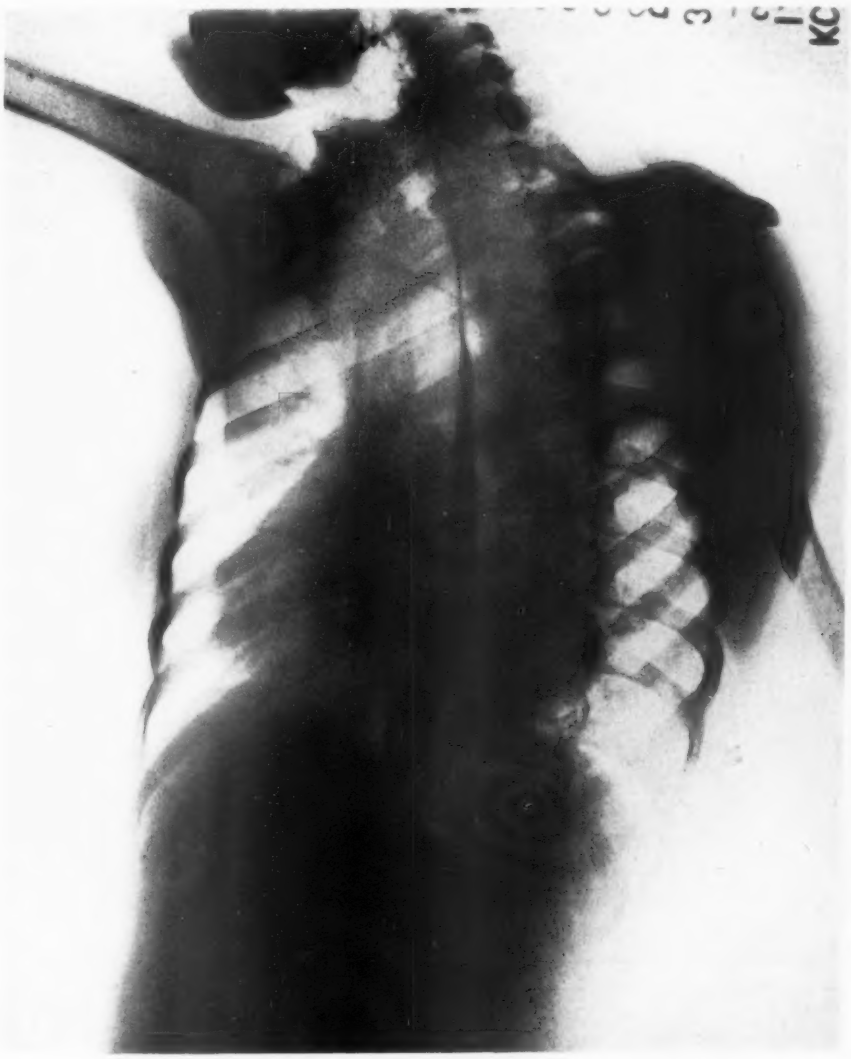

Fig. 3.—Teleroentgenogram (right anterior oblique).

TUMOR OF THE HEART

Yater[1] has recently reviewed the entire subject of tumors of the heart, and it is interesting to note that in the 143 cases of primary neoplasm of the heart that he collected, 117 of the tumors were benign and 26 malignant. The benign tumors were mainly myxomata, and most of the malignant tumors were sarcomas. He also pointed out that myxo-

mata usually arise from the endocardium of the left auricle in the region of the fossa ovalis, but occasionally from the valves. The majority of the sarcomas of the heart are situated in the auricles (more often the right, and frequently in the interauricular septum) and the pericardium. Thus, practically all primary tumors of the heart are intralocular, and could not give rise to the localized bulge which was present in this case. Secondary or metastatic tumors could be excluded by the absence of symptoms or signs of malignancy. Most heart tumors are solid, and their pulsation should be synchronous with the heartbeat, but the kymogram, in this case, revealed a reversal of pulsation in the protrusion. It is possible that a soft, very vascular tumor in the

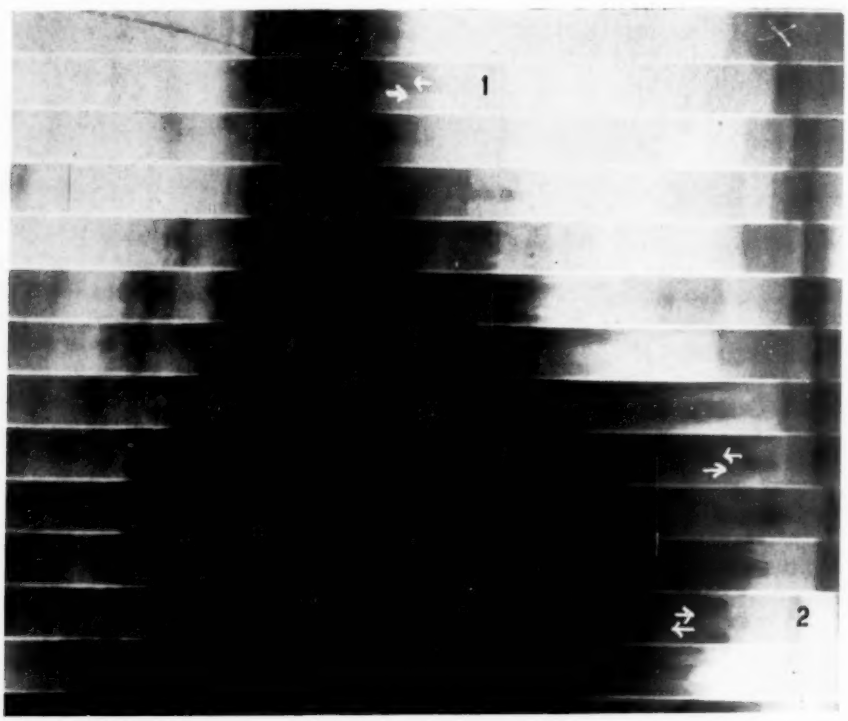

Fig. 4.—Roentgenkymogram. Ventricular pulsations may be accurately timed by comparing them with those in the descending aorta. Systole of the ventricle normally corresponds to expansion of the aorta. (1) The aortic waves. (2) The normal ventricular waves. (3) Reversal of pulsation over the involved area.

ventricular wall might so weaken it that not only would there be a bulge, but possibly also a reversal of pulsation. A tumor of the hemangiomatous type would be most likely to produce such an effect, but this tumor is very rare in the heart. In Yater's series, referred to above, there were only four cases, and in none of these was the tumor in the ventricular wall. Scott and Moore[2] reported a case of what was thought to be an aneurysm of the ventricle, but autopsy revealed a primary endothelioma invading the left ventricular wall and filling its lumen.

PERICARDIAL DEFECT

There are two main types of congenital defect of the pericardium. There may be complete absence of the pericardium, in which case the heart and lungs occupy a single cavity, or there may be a diverticulum of the pericardium. Both are rare. Abbott[3] has noted that when the pericardium is absent there is usually greatly increased mobility of the heart, occasionally hypertrophy without any of the usual etiologic factors, and, frequently, displacement of the heart to the left. A diverticulum is a thin-walled cyst, formed by the serous, or serous and fibrous, coats of the parietal layer of the pericardium, which communicates directly with the pericardial cavity. In our case, the strongest evidence against these possibilities was the fact that the roentgenkymogram showed reverse pulsations in the involved area.

ANEURYSM OF THE HEART

Finally there was the possibility of aneurysm of the heart. This is apparently an extremely rare condition in childhood. A review of the literature has revealed few reports of aneurysm of the heart at this time of life. In 1911, Herbert French[4] reported a case of traumatic aneurysm of the heart in a child of three, which resulted from a fall from a third-story window. She died twenty days following the accident, immediately after an anesthetic had been given for the reduction of a fracture. French assumed that the fall had caused a severe contusion of the heart, with hemorrhage into the myocardium, followed by softening, thinning, and, finally, rupture and hemopericardium. In 1920, Macfie and Ingram[5] reported three cases in native boys of the Gold Coast. There was no previous history of illness, and in all three sudden death occurred. The ages of the children were six, seven, and twelve; the condition was discovered at autopsy. The aneurysms were small and were located in the left ventricle near the apex of the heart (two were anterior, and one was posterior). The coronary arteries showed slight endarteritis, and they suggested that malarial endarteritis might have been an etiologic factor.

Criteria for the diagnosis of aneurysm of the heart have been suggested recently. These include the presence of a definite pulsation which is more marked between the apex and sternum than at the apex, and is associated with a muffled sound at this point. Since the advent of the roentgenkymogram it has been possible to ascertain whether the pulsations of all parts of the heart are synchronous. In cases of aneurysm, the sac expands during systole unless clot formation prevents it.

In this case, both the clinical and roentgenologic criteria for the diagnosis of cardiac aneurysm were fulfilled. In the absence of any other etiologic factor, such as trauma or coronary artery disease, and if the abnormal contour was caused by aneurysm, there must have been a congenital defect. The possibility that a soft tumor may have been infiltrating and weakening the cardiac muscle cannot be excluded.

SUMMARY

A case of localized protrusion of the left border of the heart in a twelve-year-old girl is described. The cause of this bulging was either a cardiac aneurysm of unknown etiology, possibly resulting from a congenital weakness of the muscle wall, or a soft vascular tumor of the myocardium. Both conditions are extremely rare, and a final diagnosis could not be made.

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SUBACUTE BACTERIAL (PARA-INFLUENZA) ENDOCARDITIS

A Case Report

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SUBACUTE bacterial endocarditis is considered a clinical entity, characterized by chills, fever, cardiac murmurs, embolic phenomena, clubbed fingers, and enlargement of the spleen. Pathologically, one finds valvular vegetations superimposed on a scarred endocardium or a congenitally deformed valve. The *Streptococcus viridans* is so frequently the cause of subacute bacterial endocarditis that other organisms which might produce this condition are regarded as accidental invaders, or their presence is looked upon as evidence of unusual individual susceptibility. This is a study of the development of subacute bacterial endocarditis produced by the para-influenza bacillus.

REPORT OF CASE

History.—A colored man, aged 27, was admitted to the hospital in May, 1937, complaining of chills, fever, loss of appetite, and night sweats. The patient did not recall ever having had a rheumatic infection. He developed a genital lesion in 1933 and was treated for syphilis throughout 1934. He contracted gonorrheal urethritis in 1935. This disease had apparently been arrested. There was no history of illness during 1936. Three weeks before entering the hospital the patient began to have night sweats, felt weak, and lost his appetite. He also developed daily chills, associated with fever and drenching sweats. There were shortness of breath on exertion and frequent attacks of palpitation. Gradually becoming weaker, he was sent to the hospital. The patient's past history and family history were irrelevant.

Examination.—The patient was an acutely ill, undernourished, and dehydrated colored man; his temperature was 101.6° F., his pulse rate, 110, and his respiration rate, 20 per minute. The blood pressure was 160/70. The tongue was incrusted, and the teeth were in poor condition. The neck was not rigid. Occasionally, scattered râles were heard over the bases of the lungs. The heart was enlarged; the apex was in the fifth intercostal space, 12 cm. from the midsternal line. A diffuse impulse was noted over the entire precordium. A diastolic thrill could be felt over the aortic area. A systolic and a diastolic murmur were heard over the aortic area and to the left of the sternum; they were transmitted downward. The pulse was regular, but of the Corrigan type, and pistol-shot sounds were heard over the femoral arteries. The liver and spleen could not be palpated. There was definite clubbing of the fingers. The deep and superficial reflexes appeared normal, and there were no signs of pyramidal tract disease.

Admission Laboratory Data.—The urine contained a trace of albumin; its specific gravity was 1.013; it was sugar-free; there were 4 to 5 leucocytes and 3 to 4 erythrocytes per high-power field. The erythrocyte count was 4,360,000, the hemoglobin, 89 per cent (Sahli), and the leucocyte count, 28,700; the differential count showed 83 per cent polymorphonuclear neutrophils, 14 per cent lymphocytes, and 3 per cent monocytes. The blood Wassermann and Kline reactions were negative. The nonprotein nitrogen content of the blood was 26 mg. per 100 c.c. The

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total blood protein was 4.9 grams, with 2.2 grams of albumin and 2.7 grams of globulin per 100 c.c. of whole blood. The patient's serum failed to agglutinate *Brucella abortus, Brucella melitensis, Pasteurella tularensis,* and *Bacillus proteus* X-19. A roentgenogram of the chest showed an "aortic type" of heart. The transverse diameter of the heart was 16.3 cm., and the transverse diameter of the thorax was 29.3 cm. The cardiothoracic ratio was 0.55.

Course in the hospital.—During the first ten days in the hospital the patient's temperature varied from 99 to 103° F., with frequent chills. The heart murmurs changed in pitch and quality from day to day; at times the diastolic murmur and thrill over the aortic area would be extremely harsh. On the eleventh day after admission the patient developed marked rigidity of the neck, and became very drowsy. At that time the deep reflexes were hyperactive, but there were no signs of pyramidal tract disease. Lumbar puncture revealed a yellow, turbid spinal fluid, under a pressure of 200 millimeters of water. The spinal fluid contained 104 leucocytes per c.mm., of which 89 were polymorphonuclear neutrophils and 11 lymphocytes. Blood cultures were taken on several occasions, and all revealed the para-influenza bacillus. The spinal fluid culture also developed a growth of para-influenza bacilli. The patient remained semicomatose; repetition of the blood studies during this terminal state revealed 3,150,000 erythrocytes, a hemoglobin of 40 per cent (Sahli), 13,150 leucocytes, 71% polymorphonuclear neutrophils, 1% eosinophils, 22% lymphocytes, and 1% monocytes. The patient succumbed three weeks after admission.

Clinical Diagnosis.—The clinical diagnosis was subacute bacterial (para-influenza) endocarditis and para-influenza meningitis.

AUTOPSY

The autopsy was performed by Dr. Paul Kimmelstiel, of the Department of Pathology, Medical College of Virginia.

The major pathologic changes were in the heart, lungs, and kidneys. There was an ulcerative, globular endocarditis of the aortic cusps, superimposed on an old, healed endocarditis. There were myocardial necrosis and embolic myocarditis. The kidneys were the seat of an acute, diffuse glomerulonephritis, with interstitial nephritis. There was an anemic (bland) infarct in the right kidney. The lungs revealed marked passive congestion.

The following are the details of the important pathologic changes.

Heart (Gross Description).—The heart weighed 550 gm. The right ventricular wall was 0.5 cm. in thickness. The left ventricular wall was 2.4 cm. in thickness. The epicardium was smooth and glistening; a few punctate hemorrhages were noted over the left ventricle. This ventricle was markedly injected, particularly over the left anterior portion and the base. The endocardium was smooth except for an area to be mentioned later. The pulmonary cusps and the mitral and tricuspid valves were intact. There was no thickening of the chordae tendineae or of the free edge of the visible leaflets. All three aortic cusps showed marked thickening of the free margins, which were rolled. The aortic cusps were contracted. The process of fibrous thickening involved the tissue of the commissures and encroached a few millimeters upon the aorta. Coarse verrucous vegetations were noted around the corpora arantii of the posterior cusp. The right aortic cusp was covered by a soft irregular mass of globular vegetation, measuring 2 by 1 by .08 cm. This mass was firmly adherent to the free margin of the valve and was floating freely. Just beneath the base of the vegetation there was a ragged ulceration of the aortic cusp, measuring 0.5 cm. in diameter. Both ventricles, particularly the left, were enlarged. The apex of the left ventricle was rounded. The papillary muscles were flattened, and the hypertrophy of the wall was confined to the left ventricle. The myocardium was

of a mottled, maroon color, and there were a few hemorrhages on its cut surface. In the upper, posterior portion of the interventricular septum there was an area 2.5 cm. in diameter, in which the wall was thinned; the endocardium covering it had a grayish appearance. There was slight atherosclerosis of the first part of the aorta and the coronary arteries. The coronary arteries were patent throughout.

Heart (Microscopic Description).—There were two types of changes in the sections of the heart. The first consisted of multiple, small, scattered foci of early myocardial necrosis. There was only a moderate reaction of polymorphonuclear leucocytes. These were considered as ischemic foci, caused by emboli in the smaller branches of the coronary arteries. The second type of reaction consisted of numerous smaller foci, composed of accumulated polymorphonuclear cells in areas in which the myocardium was partially or completely destroyed by liquefactive necrosis. These foci were very small and not well defined. A larger branch of the left coronary artery was the seat of an acute panarteritis, with complete destruction of the wall in one segment and diffuse infiltration of all layers by polymorphonuclear leucocytes and round cells of various types. This vessel contained a thrombus which was attached to its wall and was composed of fibrin, platelets, and polymorphonuclear cells. The myocardium was edematous, particularly throughout the perivascular trabeculae. Round cell infiltration, composed of lymphocytes and a few round cells, was seen in scattered areas beneath the endocardium.

Kidney (Microscopic Description).—Acute interstitial nephritis, associated with an early, diffuse glomerulonephritis, was noted. These changes were intracapillary in character and consisted mainly of endothelial proliferation and polymorphonuclear leucocytes within the capillary tufts. The anemic infarct was not unusual.

DISCUSSION

The para-influenza bacillus might be considered a hybrid, in the sense that it is an atypical hemolytic organism which so closely resembles hemophilus influenzae that the only differentiating features are that it requires a V factor rather than an X factor for growth, and is able to ferment maltose, saccharose, and often dextrin (Topley and Wilson[1]). It is now believed that many old recorded cases of hemophilus influenzae invasion of the endocardium were really para-influenzal in origin, because, prior to recent studies (Miles and Gray[2]), the V and X factors were not used for differentiation. There is no clinical reason for distinguishing between these hemolytic organisms, for, if they invade the endocardium, the typical syndrome of subacute bacterial endocarditis is produced. Our case was not unusual in this respect, for the clinical course was typical of subacute bacterial endocarditis.

Neither the clinical features nor the pathologic changes differ significantly from those of *Streptococcus viridans* infection. Many observers agree on this point (Horder,[3] Oppenheimer,[4] Thayer,[5] Russell and Fildes[6]). The embolic spread to the central nervous system is not unusual in subacute bacterial endocarditis (Toone[7]). A definite meningitis was recognized very early in our case.

SUMMARY

A case of infective endocarditis caused by a para-influenza organism is described. Clinical, post-mortem, and bacteriological observations

confirmed the diagnosis. This case does not differ from the usual type of subacute bacterial endocarditis.

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Department of Reviews and Abstracts

Selected Abstracts

Leo, Sidney D., Prinzmetal, Myron, and Lewis, Harvey A.: Observations Upon the Pressor Substance Causing the Rise in Blood Pressure Following the Termination of Temporary, Complete Renal Ischemia. Am. J. Physiol. **131**: 18, 1940.

The previous injection of piperidomethyl-3-benzodioxane (933F) does not prevent the rise in blood pressure which results from the re-establishment of the circulation in the completely ischemic kidney, proving that the substance responsible for this rise is not of an epinephrine-like nature.

The pressor reaction which follows the termination of complete renal ischemia is greatly reduced or abolished in animals rendered tachyphylactic to renin. This proves that the substance causing the rise in blood pressure is renin or a pressor principle having similar properties of tachyphylaxis.

The pressor effect of extracts of completely ischemic kidneys is greater than that of extracts of control normal kidneys.

AUTHORS.

Hausner, Erich, Essex, Hiram E., Herrick, J. F., and Baldes, Edward J.: Control of Coronary Blood Flow in the Heart-Lung Preparation. Am. J. Physiol. **131**: 43, 1940.

In the heart-lung preparation the influence of various factors on coronary flow was studied with the thermostromuhr. In agreement with others an intimate dependence of coronary flow on mean arterial blood pressure was found. Changes in cardiac output had no effect on coronary flow, if the arterial pressure and the temperature of the perfusing medium were kept constant. Stimulation of the cardiac branches of the stellate ganglion of the heart-lung preparation augmented coronary flow on an average of about 150 per cent. Similar values for coronary flow were obtained in the presence of a constant arterial blood pressure. The increase in coronary flow resulting from stimulation of the sympathetic nerves of the heart-lung preparation is thought to be due at least in part to a vasodilator action of the sympathetic nerves. An augmentation of coronary flow was demonstrated with acceleration of the heart rate by means of an electric stimulator. The augmented coronary flow was not due to an elevated mean blood pressure.

AUTHORS.

Asmussen, Erling: The Cardiac Output in Rest and Work in Humid Heat. Am. J. Physiol. **131**: 54, 1940.

Acclimatization to humid heat seems to involve such regulations that the circulation in rest and during work in a steady state can be kept at a practically normal level. A blood volume increased by about 5 per cent, and a slightly higher pulse rate are assumed to be the two main factors in this regulation. Circulatory

failure during work develops rather fast in humid heat owing to the fact that the heat dissipation is made difficult. A larger amount of blood is demanded for the skin circulation, making maintenance of an adequate cardiac output increasingly difficult.

AUTHOR.

Reimann, Hobart A.: Hypothermia. Subnormal Temperature and Its Relation to Neurocirculatory Asthenia (Soldier's Heart). J. A. M. A. 115: 1606, 1940.

Nine patients were studied whose temperature level was consistently subnormal. Besides hypothermia they usually had other signs and symptoms of vagotonia such as hypotension, bradycardia, palpitation, sweating, low basal metabolic rates, and numerous bizarre complaints for which no organic basis could be found. The symptoms and signs manifested by these men are the same as those described in the conditions known as neurocirculatory asthenia, effort syndrome, or soldier's heart and probably arise from similar causes. Unless patients of this type are given a correct diagnosis they may be subjected to much needless investigation and treatment and may be assigned to tasks beyond their limitations during military service. After possible organic causes for their disorder have been ruled out, treatment along psychotherapeutic and physical therapeutic lines is helpful.

AUTHOR.

Moia, Blas: The High R_3 Wave in Electrocardiogram With Ventricular Complexes of Left Type. Rev. argent. de Cardiol. 7: 129, 1940.

One hundred electrocardiograms were analyzed in which the QRS_3 of the left type not exceeding 0.10″ in duration, showed an R wave of high voltage, greater than the 25 per cent of the highest wave. A study was made of the other leads and the electrocardiographic findings were correlated with clinical conditions.

When this abnormality coincided with an R_1 wave of low voltage (with or without Q_1, without a marked S_1) sensibly lower than R_2 or when it was higher than R_2, all the patients showed cardiovascular alterations.

It was found that in certain conditions the percentage of cases with clinical signs of coronary insufficiency was very high: 77.77 per cent, when R_1 was of low voltage and much lower than R_2 (type of Q_1 of Wilson et al.); 71.42 per cent when R_3 was of unusual height, equal to the deep S_3 wave (plus minus complexes of Katz et al.); 50 per cent when R_2 of small height was accompanied by deep S_2 wave; and 22.97 per cent when there was only a left axis deviation with no other modifications.

It is pointed that the 22.23 per cent of the Q_1 classical type without a marked S_1 is observed in cases of rheumatic carditis with aortic insufficiency and coexistent mitral disease, and that, contrary to the observations of Katz et al. the wide diphasic complex was found to correspond to congenital heart disease in only 28.58 per cent of cases.

The existence of characteristic modifications of Lead III and their close correlation with clinical signs of coronary insufficiency give diagnostic value to the anomaly described.

The pathologic significance of triphasic complexes with high R_3 is discussed and the influence of respiratory movements on R_3 wave are analyzed.

AUTHOR.

öhnell, Richard F.: Post Mortem Examination and Clinical Report of a Case of the Short P-R Interval and Wide QRS Wave Syndrome. Cardiologia 4: 249, 1940.

I have presented the pathologic anatomy and other data from a case of the type, the clinic of which was described by Wolff, Parkinson, and White in 1930.

Our patient succumbed suddenly to a heart attack. In the myocardium, round cell infiltration (one of the foci bordering the left ventricular branch of the A-V bundle) and an increased amount of connective tissue and brown atrophy were microscopically found. The theories proposed for the WPW syndrome are discussed and a special type of coupled ventricular premature beats are suggested as an explanation.

AUTHOR.

Scherf, David, and Weissberg, Jonas: The Electrocardiogram After Intravenous Injection of Hypertonic Sucrose and Saline Solutions. Cardiologia **4**: 260, 1940.

Hypertonic sucrose and saline produce definite electrocardiographic changes in the majority of patients with angina pectoris. In view of the fact that precordial pain frequently develops in such patients after the intravenous injection of these solutions, it may be assumed that the reason for the electrocardiographic changes and the pain is a relative myocardial ischemia immediately after the introduction of these solutions into the general circulation. The action of these hypertronic solutions consists of an increase in blood volume without a comparable increase in myocardial blood supply. This is the consequence of an osmotic action.

AUTHORS.

Dressler, Wilhelm, and Pfeiffer, Robert: Cardiac Aneurysm. A Report of Ten Cases. Ann. Int. Med. **14**: 100, 1940.

Ten cases are reported in which the diagnosis of cardiac aneurysm was made during life. In two of these cases the diagnosis was verified by post-mortem examination, while five cases characteristic radiologic findings were obtained.

The diagnosis of cardiac aneurysm is based primarily on physical examination. On palpation one finds a large and forceful cardiac thrust, which, depending upon the site of the aneurysm, is located either within the mid-clavicular line or outside of it, and most commonly at the level of the fifth rib. The diffuse character of the thrust, its considerable width, and particularly its medial extension, are significant features in diagnosis. The area of pulsation is likely to be situated more craniad than one would expect for the apical thrust caused by an hypertrophied left ventricle. Such a pulsation is of significance for the diagnosis of cardiac aneurysm, if the history and the electrocardiographic findings indicate a preceding cardiac infarction, and if other causes for such a forceful cardiac thrust, such as hypertension or mitral and aortic valvular lesions, can be excluded. It is especially significant if the development of such a pulsation can be observed subsequent to a coronary artery occlusion.

In our material we have not observed murmurs nor any particular findings obtained by means of percussion.

The radiologic examination revealed characteristic features in only half of our cases. This should be explained by the fact that the aneurysmal development is most often limited to the apical portion of the heart. This location results merely in an elongation of the apical portion of the silhouette, such a finding being not characteristic in any way. Pathognomonic findings in the roentgenogram, however, may be expected for those cases where the aneurysmal formation involves the basal or middle portions of the left ventricle. One may then expect to find along a part of the left lower cardiac contour one or the other of the following findings: a localized bulge, a sudden kink, a centrifugal, systolic pulsation, calcification, shell-like in arrangement. The esophagus may reveal in its lower third either an impression from in front or a shallow deviation dorsad.

Electrocardiographic alterations indicating cardiac infarction were well marked in all of our cases and remained unchanged over a course of years. A deep S deflection in Leads II and III was strikingly noted in one-half of the cases.

The prognostic outlook in the presence of cardiac aneurysm is relatively favorable. This refers both to expectation of life and to effort capacity.

AUTHORS.

Graham, H. Boyd: Rheumatic Heart Disease. M. J. Australia **2**: 101, 1940.

A classical description of rheumatism in childhood is presented in the form of extensive extracts from Cheadle's Harveian Lectures of 1889.

Additional features of outstanding importance are outlined; they have been added to our knowledge of the subject since Cheadle's time.

It is advanced as a plausible theory, arrived at by inference from other workers' published results, that the initial hemorrhagic lesions of rheumatic affections lead to reactionary developments which comprise the general and special pathology of the disease.

AUTHOR.

Brown, Morton G., and Wolff, Louis: Recovery From Acute Rheumatic Fever Without Permanent Cardiac Damage. New England J. Med. **223**: 242, 1940.

Fifty per cent of a group of 175 patients with acute rheumatic fever showed no evidence of heart disease after follow-up periods averaging seven years.

There is no constant relation between the severity of the illness or the number of recurrences and the development of cardiac damage.

Patients who show no permanent organic heart changes following the first attack of rheumatic fever are prone to escape permanent injury despite further attacks.

The final evaluation of the state of the valves must be delayed for several years after an attack of rheumatic fever.

AUTHORS.

Swift, Homer F.: Public Health Aspects of Rheumatic Heart Disease. Incidence and Measures for Control. John H. Wycoff Lecture for 1939-40, J. A. M. A. **115**: 1509, 1940.

The size of the problem of rheumatic heart disease, from the standpoint of public health, indicates the desirability of widely extending the facilities for meeting the situation. The long period usually consumed in the evolution of rheumatic heart disease offers opportunity for interfering with that evolution at various times. Those unfavorable factors classified as economic are subject to improvement. Favorable climatic factors may be utilized. Because functional trauma of cardiac tissues harboring rheumatic inflammation probably increases the damage to these tissues, prolonged rest for such actively diseased structures is requisite and should be provided on a scale commensurate with the size of the problem. The role of hemolytic streptococcus infections in initiating the disease rheumatic fever and in inciting relapses indicates the importance of protecting these patients from such infections. When these elements in a public health program are clearly recognized, there can be little doubt of its establishment.

AUTHOR.

Kuttner, Ann G.: The Effect of Large Doses of Vitamins A, B, C and D on the Incidence of Upper Respiratory Infections in a Group of Rheumatic Children. J. Clin. Investigation **19**: 809, 1940.

No evidence was obtained to suggest that the addition of large doses of vitamins A, B complex, C, and D to an ordinary well-balanced diet reduces the incidence of upper respiratory infections.

Three children who had received the additional vitamins for a considerable period of time developed rheumatic symptoms following an attack of streptococcus pharyngitis.

Children on the regular diet without additional vitamins and those on the regular diet with additional vitamins gained weight at approximately the same rate during the five-month period.

AUTHOR.

Roth, Irving R.: Clinical Aspects of Rheumatic Fever in Adults. Bull. New York Acad. Med. **16**: 514, 1940.

Rheumatic fever in adults does not seem to conform to a distinctive pattern, and the polyarthritic picture suggested by hospital records is more apparent than real. At any rate, it does not represent the whole disease. Smoldering forms are not uncommon and it is this form that probably precipitates insidious failures of the circulation. It is probably responsible also for auricular fibrillation in some cases.

The anatomic lesions in the younger adults are generally multiple but, as age advances, those with combined mitral and aortic lesions are seemingly weeded out. Chances for survival seem best for those who have mitral lesions alone.

Auricular fibrillation, except as a terminal event, is rare in early adulthood. However, as age advances, it soon becomes the dominant arrhythmia and may be present in from 20 to 25 per cent of patients past 40 years of age.

Functional capacity in young adults is generally excellent despite multiple valvular lesions. At middle age or beyond, it is on the decline and heart failure is an ever-present threat.

Accompanying diseases are of minor importance in the younger adult with a rheumatic cardiac condition. The greatest hazard is an acute rheumatic episode. At middle age, on the other hand, an accompanying hypertension seems to be the most embarrassing complication.

Emotional factors are present in both groups and color the clinical picture appreciably. Not only symptoms but also physical signs and, in a measure, even prognosis are influenced by them. They must be taken into serious account in any attempt to appraise the clinical aspects of rheumatic heart disease in adult life.

AUTHOR.

Kampmeier, R. H., and Combs, Stuart R.: The Prognosis in Syphilitic Aortic Insufficiency. Am. J. Syph., Gonor. & Ven. Dis. **24**: 578, 1940.

An analysis has been made of 163 cases of syphilitic aortic insufficiency studied at Vanderbilt University Hospital. One hundred and twenty, or 73 per cent, of the patients are dead; 54.6 per cent of the deaths occurred within three years after the onset of symptoms.

The importance of race and sex in the prognosis of syphilitic aortic insufficiency is clearly indicated by this study. Only one-fourth of the negro males with syphilitic aortic insufficiency survived three or more years after the appearance of symptoms, whereas slightly less than one-half of the white males and negro females, and over one-half of the white females survived three or more years.

Occupations involving manual labor are conducive to poor prognosis in syphilitic aortic insufficiency.

As is to be expected, the chance finding of asymptomatic syphilitic aortic regurgitation at the time of initial examination occurred more frequently in patients who are still living.

Moreover, the presence of congestive heart failure and evidence of free aortic regurgitation was noted more frequently in patients who experienced, subsequently, short survival periods.

The longer the duration of symptoms of syphilitic aortic insufficiency before the diagnosis becomes established, the poorer the prognosis.

This study does not indicate that adequate antisyphilitic treatment influences favorably the prognosis of syphilitic aortic insufficiency.

AUTHORS.

Ayman, David, and Goldshine, Archie D.: Blood Pressure Determinations by Patients With Essential Hypertension. I. The Difference Between Clinic and Home Readings Before Treatment. Am. J. M. Sc. 200: 465, 1940.

Thirty-four patients with various degrees of essential hypertension had their blood pressure studied over a long period in the clinic and at home. The home readings have been taken very carefully twice daily for weeks or months by the patient or a member of the household. This study shows that the home systolic and diastolic blood pressure readings are lower than the clinic readings in all cases of essential hypertension. In 30 per cent of the cases the systolic home blood pressure readings were 40 mm. or more lower than those in the clinic, and in 24 per cent the diastolic home readings were 20 mm. or more lower than the clinic readings. The method caused no neurosis or harm in any patient. Those patients with only slight difference between home and clinic readings had, in general, comparatively little fluctuation of blood pressure from day to day. The home blood pressure method should be of value to teach the patient the nature of his disease, to help the physician observe better the natural course of the disease, to aid in the prognosis of the individual case, and to permit the clear-cut evaluation of therapy.

AUTHORS.

Saphir, Otto, and Ballinger, Joseph: Hypertension (Goldblatt) and Unilateral Malignant Nephrosclerosis. Arch. Int. Med. 66: 541, 1940.

Three cases of severe arterial hypertension secondary to unilateral renal vascular stenosis, with consequent ischemia of one kidney, are reported. In two of these, autopsy revealed unilateral malignant nephrosclerosis (arteriolonecrosis). Because of recent experimental evidence, this unique observation could be explained readily. From his experimental studies, primarily concerned with the production of arterial hypertension by clamping the renal arteries in the dog, Goldblatt concluded that both hypertension and renal insufficiency are the minimal prerequisites for the induction of arteriolonecrosis, for in the absence of either of these factors no necrotizing changes are observed. The patients in both these cases had severe arterial hypertension brought about by renal artery changes, with resulting ischemia of one kidney. Both subsequently had renal excretory insufficiency. This was precipitated in one instance by the onset of congestive heart failure and in the other by the development of acute ascending pyelonephritis in the kidney opposite the ischemic one. Because of the presence of the severe arterial hypertension and excretory renal insufficiency, the arterioles in the contralateral kidneys (with a patent vascular system) showed necrotic changes, and these kidneys presented the typical picture of malignant nephrosclerosis. The arterioles in the ischemic kidneys revealed no necrotic changes because the stenosis of the renal and intrarenal arteries militated against the presence of severe hypertension within the arterioles. Thus, the pathogenesis of the malignant nephrosclerosis in these cases is exactly similar to that of the arteriolo-

necrotic changes produced experimentally by Goldblatt. The third case was included in this report for comparative purposes. This patient died of intercurrent bronchopneumonia and never showed evidences of renal insufficiency. In this instance the requisite factors for development of the malignant phase of hypertension were lacking, and, as was expected, there was no evidence of arteriolonecrosis on post-mortem examination.

AUTHORS.

Odel, Howard M.: Structural Changes in the Arterioles of the Myocardium in Diffuse Arteriolar Disease With Hypertension Group 4. Arch. Int. Med. 66: 579, 1940.

The results of this study indicate that, in the presence of diffuse arteriolar disease with hypertension group 4, structural changes in varying degrees of severity occur in the arterioles of the myocardium.

Wide variation from case to case was noted in the nature and degree of change. Increase in the medial nuclei seemed to be an early change, with hyperplasia of the internal elastic lamina, intimal proliferation, and degenerative changes occurring later in the process. It is a significant fact that structural changes in the myocardial arterioles were not observed in all cases and that, when they did occur, the changes were similar to those occurring in other organs in the same case, although less pronounced.

The analysis of the clinical features in this series of cases indicates that the syndrome of malignant hypertension is a clear-cut clinical entity and that the clinical picture may be characterized by symptoms predominantly cerebral, cardiac, or renal, or by any combination of the three.

Not only was there wide variation in the occurrence and degree of severity of the histologic changes among individual patients, but there was a striking difference in the degree of involvement between different vessels of the same patient and between different segments of the same vessel.

From the evidence presented here from data collected by others, it appears that malignant hypertension is a diffuse arteriolar disease in every sense of the term and that no organ which is subjected to elevation in systemic blood pressure can escape entirely. Why structural changes in the arterioles of the myocardium do not progress at the same rate or to the same degree as do similar changes in the arterioles of other organs is a question which has yet to be answered.

AUTHOR.

Hildebrand, Alice G., Montgomery, Hamilton, and Rynearson, Edward H.: Necrobiosis Lipoidica Diabeticorum. Arch. Int. Med. 66: 851, 1940.

Seventy-eight cases of necrobiosis lipoidica diabeticorum which have been described in the literature since the first report of this dermatosis by Oppenheim, in 1929, are reviewed. Observations on eight cases of necrobiosis lipoidica diabeticorum encountered at the Mayo Clinic since 1936 are related. More than 87 per cent of all the patients, both those seen elsewhere and those seen at the clinic, had diabetes mellitus, and in eight typical cases of necrobiosis, evidence of diabetes mellitus was not found. In the majority of the cases in the entire series, the cutaneous lesions had developed from several months to as long as seventeen years after the onset of diabetes, although in about 18 per cent of the cases encountered elsewhere and 25 per cent of those encountered at the clinic the reverse was true, the cutaneous lesions preceding the onset of the diabetes by as long as eight years. All patients were white, and more than 80 per cent were women. The most common age of onset among all patients was between 10 and 40 years.

In those who had diabetes mellitus, the constitutional disease in most instances could be called moderately severe to severe, and in most of them the diabetes had been poorly controlled. Trauma apparently played a definite role in the development of the cutaneous lesions in several cases.

The lesions in this condition are most often reddish papules or yellowish plaques with well-defined reddish-brown borders, much infiltration, and central telangiectasia. They usually occur on the lower parts of the legs. Microscopically the lesions are characterized by changes in the deep layers of the cutis, consisting of necrobiotic regions in which there are granular degeneration of the collagen fibers, loss of elastic fibers, and extracellular deposition of various lipoids, surrounded by a region in which the arterioles show intimal proliferation and perivascular myocytic infiltration. The absence of xanthoma or foam cells containing cholesterol and cholesterol esters differentiates these lesions from those of the other xanthomatoses except lipoid proteinosis, which represents a different clinical picture. Quantitative determinations of the lipoid constituents of these lesions were suggestive of a relative increase of lecithin in the tissues.

Studies of the blood lipoids have shown that in the majority of all cases encountered elsewhere and in all of the cases encountered at the clinic the values lay within normal limits. The lesions tended to run a chronic course, and neither local therapy nor, in the case of diabetic patients, general management tended to speed their healing. In some cases the lesions slowly receded and left depressed scars.

Two ideas regarding the pathogenesis of this condition have been considered: (1) that which assumes the occurrence of a primary vascular injury, possibly by circulating toxins, with secondary thrombosis, necrosis, and fat imbibition; and (2) that which assumes a local lipoid disturbance in the skin, based on a general disturbance in fat metabolism. Neither hypothesis has proved satisfactory in the light of studies made both here and elsewhere. Therefore, the pathogenesis of this condition remains obscure.

AUTHORS.

Ravenna, Paolo: Banti Syndrome (Fibrocongestive Splenomegaly): Definition, Classification and Pathogenesis. Arch. Int. Med. 66: 879, 1940.

Evidence has been accumulating which supports the view that Banti splenomegaly is largely due to splenic congestion and that this congestion is not dependent on an obstructive factor in the portal-venous bed. It is suggested that the congestion may be due to primary lesions of the small splenic arteries which regulate the blood flow into the spleen (''primary active congestion'').

The human spleen should be considered as an elastic rather than a contractile organ. Its variations in size depend on variations in volume of the inflowing blood, rather than on active contractions of the smooth muscle of its supporting framework.

From a mechanical point of view, the spleen might be defined as an automatic controller which regulates the pressure of the splenic venous blood in order to maintain the balance between the volume of inflowing blood and the amount which can be discharged through the hepatic resistance. Normally, and within certain limits, in pathologic conditions, the splenic elasticity guarantees a pressure sufficient to secure the further progress of venous portal blood. Congestive splenic enlargement is therefore a mechanism to counterbalance either increased volume of portal blood or increased peripheral resistance to the discharge of a normal amount of blood.

The Banti syndrome is a symptom complex dominated by chronic fibrocongestive splenomegaly, accompanied by portal hypertension and complicated by,

or associated with, hepatic cirrhosis or thrombosis of the splenic and portal veins. It may depend on various causative agents, either infective or toxic. A scheme for its etiological classification is presented.

The splenic changes of the Banti syndrome are probably due to primary lesions of the splenic arterioles, the regulating power of which becomes insufficient to control the inflow of blood. The consequent congestive splenomegaly is the cause of the circulatory disturbance in the portal bed. Secondarily, hepatic cirrhosis and venous thrombosis may aggravate the state of portal circulation.

AUTHOR.

Levitt, Abel, and Levy, Dexter S.: Luetic Meso-Aortitis With Aneurysm of the Thoracic and Abdominal Aorta. Am. J. Clin. Path. **10**: 332, 1940.

A case of vascular syphilis is reviewed in which there was an unusually large thoracicoabdominal aneurysm. This aneurysm apparently developed about twenty years after the primary lesion, progressed rather rapidly in its last year to involve the spinal cord by pressure, and finally terminated by rupture into the peritoneal cavity.

AUTHORS.

Ronald, James, and Leslie, Margaret: Thrombosis of the Abdominal Aorta. Glasgow M. J. **84**: 7, 1940.

A case of complete thrombosis of the abdominal aorta is reported. The condition was unaccompanied by localizing signs, and occurred in a man aged 43 years who was the subject of hypertensive and syphilitic disease.

Of particular interest in this case was the almost complete lack of "regional" signs and symptoms. Apart from the sudden acute abdominal pain and the gripping feeling in the legs, there was little to distinguish it from any other case of severe hypertension. Although autopsy failed to reveal the establishment of a collateral circulation, there was no clinical evidence of impaired circulation in the extremities. It is difficult to understand how such an extensive lesion as was present in the aorta can be unaccompanied by localizing signs.

AUTHORS.

LeRoy, George V., and Speer, John H.: A Comparison of the Coronary Vasodilator Activity of Certain Alkyl Xanthines. J. Pharmacol. and Exper. Therap. **69**: 45, 1940.

The activity of a series of newly conceived xanthine derivatives has been investigated, using the outflow of blood from the coronary sinus of an intact, anesthetized dog as an indicator. The results of the study of these drugs are reported.

Sodium salts of three of the new compounds: 1,3, dimethyl, 8, ethyl xanthine; 1,3, diethyl, 8, methyl xanthine; and 1,3, diethyl xanthine, augment the coronary sinus outflow to an extent that exceeds the increase observed when sodium salts of theophylline and theobromine are employed.

It is demonstrated, but not explained, that the ethylene diamine salt of theophylline is twice as active as the sodium salt. For theobromine, the difference is even greater; and the sodium acetate compound is five times as effective as the sodium salt. The coronary vasodilator effectiveness of the experimental sodium salts of the alkyl xanthines studied is inferior to the activity of the familiar therapeutic compounds, theophylline ethylene diamine, and particularly, theobromine sodium acetate.

AUTHORS.

Grollman, Arthur, Harrison, T. R., and Williams, J. R.: Therapeutics of Experimental Hypertension. J. Pharmacol. and Exper. Therap. **69**: 76, 1940.

The effect of sodium nitrite, potassium thiocyanate, erythrol tetranitrate, Allium sativum, acetyl-β-methylcholine, sodium chloride, and renal extract on the blood pressures of hypertensive rats was investigated. The blood pressure was reduced to normal levels following the administration of renal extract. None of the so-called "depressor" or "hypotensive" substances manifested an ability to reduce appreciably the blood pressure, and their clinical value is thus questionable. The administration of a relatively large dose of sodium chloride did not markedly elevate the blood pressure.

AUTHORS.

Gottdenker, F., and Wachstein, M.: Circulatory Effects of the Venom of the Indian Cobra (Naia Naia). J. Pharmacol. and Exper. Therap. **69**: 117, 1940.

In cats and rabbits the intravenous injection of a small dose of cobra venom (6 to 9μ grams per kilogram) causes a long lasting rise of arterial blood pressure, occasionally preceded by an evanescent depressor effect. When the blood pressure has returned to normal the injection of a second similar dose of venom is ineffective (tachyphylaxie).

Cobra venom causes vasoconstriction in the rabbit's ear perfused with physiologic salt solution and there is no, or only little, diminution of the effect by repeated administration of the venom.

In the heart-lung preparation of the dog the injection of cobra venom (60μ grams) produces long lasting dilatation of the coronary vessels which can readily be desensitized against the venom by a previous injection of a subthreshold dose.

The intravenous injection into cats of 9μ grams of cobra venom per kilogram produces profound alterations in the electrocardiogram.

Cobra venom causes systolic standstill of the auricular strip (rabbit's and guinea pig's heart) and of the fiber of Purkinje (dog's heart). No tachyphylaxie could be obtained in these preparations.

In the isolated frog's heart cobra venom causes irreversible systolic contracture. During the development of the contracture the electrocardiogram shows signs of impairment of conduction, shortening of the duration of the systole and changes in the QRS complex and T wave. The absence of calcium ions in the perfusion fluid alters the response. The muscle becomes less sensitive to the venom which produces stoppage of beat without signs of systolic contracture.

AUTHORS.

Gold, Harry, Kwit, Nathaniel T., and Cattell, McKeen: Studies on Purified Digitalis Glucosides. I. Potency and Dosage of "Digitaline Nativelle" by Oral Administration in Man. J. Pharmacol. and Exper. Therap. **69**: 177, 1940.

Digitalis leaf was compared with "Digitaline Nativelle" in a selected group of forty-nine patients, some with auricular fibrillation and others with regular sinus rhythm, in a series of experiments which extended in individual cases over periods of from twenty-four to fifty-four weeks.

The results of animal bio-assay methods (frog and cat method) for purified digitalis glucosides are not transferable to man. Their potency must be determined on man directly. Possible reasons for the discrepancies are not discussed.

A method has been described for the assay of digitalis preparations in man, comparing a standard with an unknown preparation in the same individuals.

For the assay of digitalis in man, either RT-T changes in the electrocardiogram in subjects with normal sinus rhythm or ventricular rate changes in those with auricular fibrillation may be used to detect the amount of digitalis action. The two methods yield similar results and reflect the therapeutic potency of digitalis glucosides.

"Digitaline Nativelle" is about 200 times as potent as digitalis by the cat and frog methods, but 1800 times as potent when the two are compared in man.

It requires from 6 to 12 cat units of digitalis leaf to produce the effects of 1 cat unit of "Digitaline Nativelle" by oral administration.

Details of the dosage of "Digitaline Nativelle" are discussed. Full digitalization is accomplished by a total of 3 cat units by mouth, whereas for digitalis it requires about 25 cat units.

A safe method has been described for the determination of the ratio of toxic to therapeutic potency of digitalis preparations in man. The results show that this ratio is similar for digitalis leaf and "Digitaline Nativelle."

Attention has been called to the marked variability in the strength of U.S.P. XI tinctures of digitalis and to the possibility of the use of purified digitalis materials of more constant potency which may require no animal bio-assay.

AUTHORS.

Miller, Edgar R.: Use of Heparin in Treating a Case of Subacute Bacterial Endocarditis With Patent Ductus Arteriosus. Delaware State M. J. **12:** 155, 1940.

An 11-year-old girl with subacute bacterial endocarditis was treated with heparin by the continuous drip method for ten days by transfusion with stored citrated blood and sulfapyridine. The venous clotted time rose the first day from four minutes to four hours twenty-five minutes. She died suddenly on the tenth day of treatment.

Autopsy showed an extensive fresh brain hemorrhage into the lateral ventricle, extending through the third and fourth ventricles to the basal cisternae. There was a patent ductus arteriosus with vegetations or scarring. There was an old mitral valve lesion probably rheumatic in origin; there were fibrous vegetations of subacute bacterial endocarditis. There was evidence that an embolus had been washed off this lesion.

MCCULLOCH.

Stoll, Arthur: The Genuine Cardiac Glucosides. J. Am. Pharm. A. **27:** 761, 1938.

This discussion has dealt with attempts to isolate the active principles of drugs in pure form without destroying their natural initial state. Only a few examples in the very specialized and limited field of cardiac glucosides have been given. There are doubtless many other cases where the genuine active principles of drugs are not yet known, and therefore, a vast field for investigation still remains.

AUTHOR.

Corrigendum

The heading of the last abstract on page 646 in the November issue should read **Sosman, Merrill C.: Subclinical Mitral Disease.** J. A. M. A. **115:** 1061, 1940, instead of **Symonds, C. P.: Cerebral Thrombophlebitis.** Brit. M. J. p. 348, Sept., 1940.

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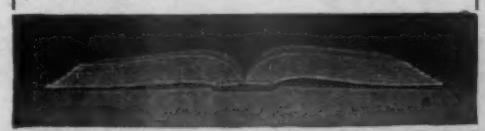

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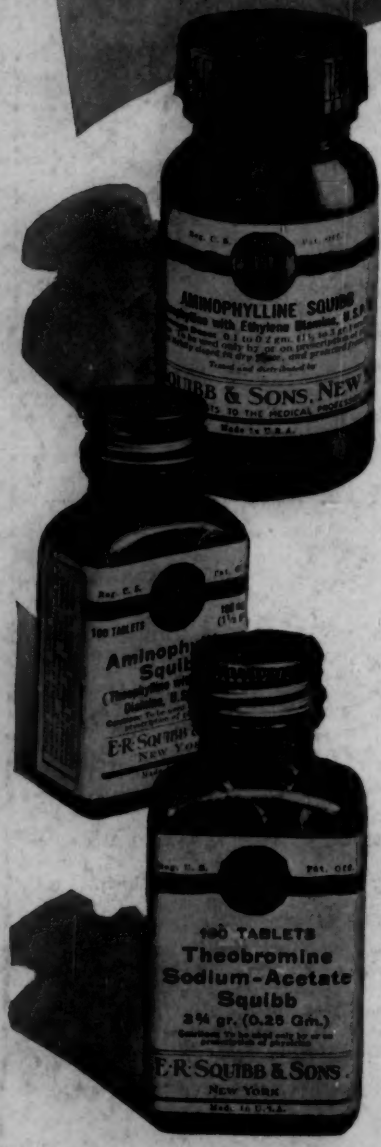

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